Pergamon

Tetrahedron Vol. 51, No. 6, pp. 1535-1573, 1995

0040-4020/95 $29.00+0.00

0040-4020(94)01019-6

TETRAHEDRON REPORT NUMBER 365

A Consideration of the Barrier for Carbocation-Nucleophile Combination Reactions

John P. Richard

Department of Chemistry, University at Buffalo, SUNY, Buffalo, NY 14260

Contents

1. INTRODUCTION

The additions of nucleophilic reagents to carbocations are among the simplest reactions in organic chemistry and studies on the mechanism for these reactions and their interpretations have played an important role in the development of physical organic chemistry. The results of early studies on carbocation-nucleophile combination reactions led to two simple and important generalizations: the kinetic reactivity of carbocations towards nucleophilic reagents increases with increasing thermodynamic driving force for the nucleophile addition reaction, and the selectivity for reactions of carbocations with reagents of different nucleophilicity decreases with increasing thermodynamic driving force. These reactions have been the subject of continued interest, with the result that several notable failures of earlier generalizations have been reported. Apparently, unusually small or large rate constants, respectively, are observed for nucleophilic addition of solvent to 4-methoxybenzyl carbocations that are destabilized by a strongly electron-withdrawing substituent or stabilized by a strongly electron-donating substituent.[1,2] Constant nucleophile selectivities are observed for large variations in the thermodynamic stability of substituted triarylmethyl carbocations and related electrophiles,[3,4] and constant selectivities are observed for the addition of alkyl alcohols to a wide range of α-substituted 4-methoxybenzyl carbocations.[5]

The original observation that the results of studies on carbocation-nucleophile combination reactions lend themselves to simple generalizations was satisfying and provided confidence that the mechanisms for more complex reactions might also be understood. However, the exceptions to these generalizations show that it is dangerous to assume that even simple reaction mechanisms can be easily understood. These exceptions have the potential to provide new insight into the mechanism for covalent bond formation at electron-deficient trivalent carbon. However, this potential has not been fully realized, and there is at present no generally accepted model that rationalizes the large body of experimental data on substituent effects on carbocation-nucleophile combination reactions.

One problem has been a lack of communication between experimental chemists, who concentrate on gathering data but lack the skills to model their results using the highest levels of modern theory, and theoretical and computational chemists. The present review summarizes the results of recent experimental studies on carbocation-nucleophile combination reactions from the author's laboratory, along with other pertinent results. A qualitative descriptive model developed during the course of this work that rationalizes these results will be presented, with the hope that it will serve as a point of departure for the development of more rigorous models.

2. ORIGIN AND NATURE OF THE KINETIC BARRIER TO THE ADDITION OF NUCLEOPHILES TO CARBOCATIONS

2.1. Polar and Resonance Substituent Effects

It is generally accepted that, subsequent to geometric alignment that permits bond formation, encounter complexes of the methyl carbocation with nucleophilic reagents proceed directly to products, without passage over an energy maximum (Figure 1). That is, these complexes also serve as the transition state for addition of the nucleophile. So long as the overall reaction is thermodynamically favorable, electrostatic or inductive stabilization of the carbocation by electron-donating substituents would not be expected to create a barrier to nucleophile addition, because there will be equal expression of the stabilizing polar effect in both the reactants and the early transition state, whose structure is essentially identical to that of the reactants.

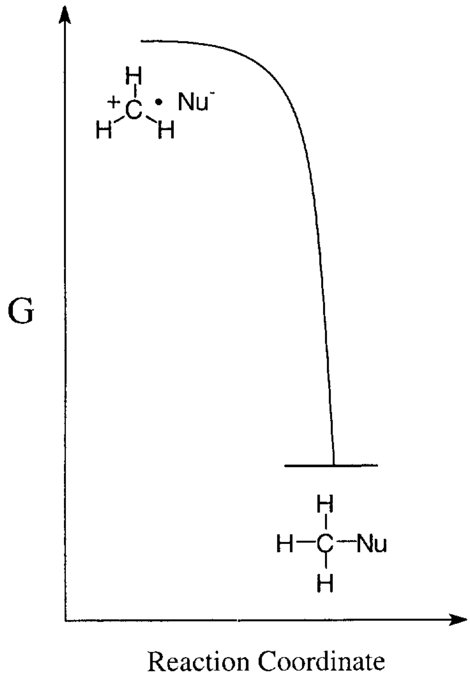
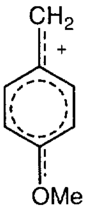


Figure 1. Reaction coordinate profile for the barrierless reaction of a nucleophile with the methyl carbocation.

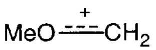
A barrier to carbocation-nucleophile combination appears with progressive stabilization of the methyl carbocation by resonance electron-donating substituents. For instance, there is probably a small barrier to the addition of 50/50 trifluoroethanol/water to the benzyl carbocation ($k_s \approx 4 \times 10^{11}$ s^{-1}),[6-9] and there is direct evidence for a chemical barrier to addition of this solvent to the 4-methoxybenzyl carbocation (**1**, $k_s = 2 \times 10^8$ s^{-1}).[9] A small barrier probably exists for addition of water to the methoxymethyl carbocation (**2**, $k_s \approx$ 10^{12} s^{-1}).[10] Substitution of an α-sulfur for an α-oxygen (**3**),[11] or an α-azido for an α-methoxy group (**4**),[12] leads to substantial increases in the lifetimes of α-substituted 4-methoxybenzyl carbocations in aqueous trifluoroethanol, so that significant barriers are also expected for addition of this solvent to **3** and **4**.

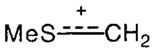
It is significant that the effects of strongly π-electron-donating 4-methoxyphenyl, methoxy, and methylthio substituents are expressed in the reactant-like transition state for addition of nucleophiles to the methyl carbocation (Figure 1), and this should focus our attention on the profound effect of the partial π-bond on the structure and reactivity of carbocations. It is difficult to quantify these partial-bond orders or strengths. However, the following results from experimental and theoretical studies show that valence bond structures with π-bonds at the cationic center make important contributions to the structures of **1-4**.

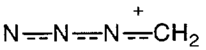
(1) AM1 calculations show that the increase in positive charge at the oxygen of 4-methoxybenzyl chloride upon ionization to form **1** (0.075 units) is 60% as large as the increase in charge at the benzylic carbon (0.129 units).[13] There must also be appreciable delocalization of charge onto the *ortho* ring carbons of **1**, so that more than 37% of the positive charge at **1** is delocalized onto the aromatic ring.



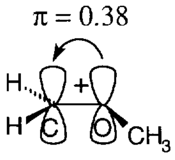
1

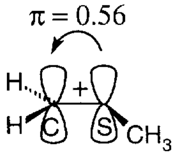

$\mathrm{MeO}\overset{+}{\text{- - -}}\mathrm{CH_2}$ **2**


$\mathrm{MeS}\overset{+}{\text{- - -}}\mathrm{CH_2}$ **3**


$\mathrm{N}\text{- -}\mathrm{N}\text{- -}\overset{+}{\mathrm{N}}\text{- -}\mathrm{CH_2}$ **4**

(2) The structures of the methoxymethyl and methylthiomethyl carbocations determined by *ab initio* calculations show significant partial π-bonds that result from transfer of 0.38 and 0.56 π-bonding electrons, respectively, from the heteroatom to the cationic center.[14]

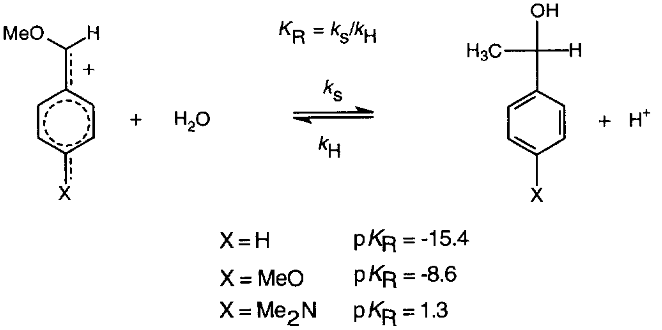




(3) The 4-methoxy and 4-dimethylamino substituents stabilize the

1-phenylethyl carbocation towards the addition of water by 9 and 23 kcal/mol, respectively (Scheme 1).[15] [The pK_R for the 1-(4-dimethylaminophenyl)ethyl carbocation was calculated from the rate constant ratio k_s/k_H using $k_s = 40\ s^{-1}$ for capture of this carbocation by water.[46] This value for the pK_R should replace an earlier lower limit[15] calculated using $k_s \leq 2000\ s^{-1}$]. While I am not aware of a simple relationship between the magnitude of these substituent effects and the strength of the partial π-bond to the benzylic carbon, the large observed effect of the *N,N*-dimethylamino substituent strongly suggests a pronounced iminium ion character for the 1-(4-dimethylaminophenyl)ethyl carbocation. This 23 kcal/mol stabilization energy for the 4-dimethylamino substituent is a significant fraction of the energy of a π-covalent bond, and there is probably an even larger fractional π-bond character at nitrogen and the benzylic carbon, because part of the driving force for electron delocalization must be used to overcome the unfavorable loss of aromaticity associated with the addition of 2π electrons to the 6π Hückel aromatic system.

(4) The Brønsted reaction constant for addition of alkyl alcohols to 4-substituted 1-phenylethyl carbocations increases from $\beta_{nuc} = 0.16$ to $\beta_{nuc} = 0.50$ as the substituent is changed from 4-methyl to 4-dimethylamino.[16] While there is no simple relationship between β_{nuc} and resonance stabilization of these electrophiles, the size of this change in β_{nuc} is striking and suggests that there are profound changes in structure of these benzylic cations and the transition states for the nucleophilic addition reactions on changing from weakly to strongly π-electron-donating ring substituents (see Section 4.2).



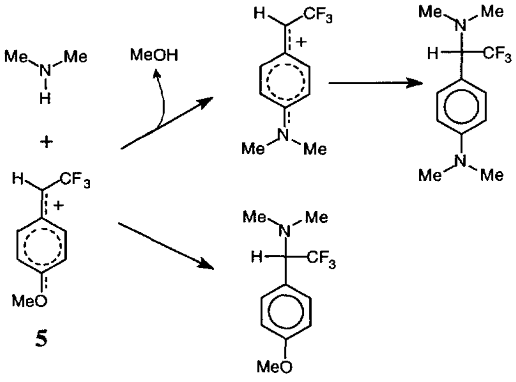
Scheme 1

The strongly electron-withdrawing trifluoromethyl group establishes a large, destabilizing, charge-dipole interaction with the cationic center when it is attached to the benzylic carbon of **1**. This interaction is partly relieved by charge delocalization onto the aromatic ring, because electronic reorganization increases the separation of the interacting electron-deficient centers. The following observations show that there is extraordinarily large charge delocalization in α-trifluoromethyl-substituted 4-methoxybenzyl carbocations, which confers on these species properties not normally associated with benzylic carbocations.

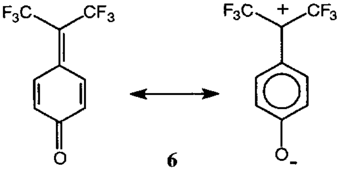
(1) AM1 calculations of charge show a net increase in *negative charge* at the benzylic carbon upon ionization of α,α-di(trifluoromethyl)-4-methoxybenzyl chloride to form the α,α-di(trifluoromethyl)-substituted 4-methoxybenzyl carbocation.[13] Ionization of this substrate also causes a large increase in the electrophilic reactivity of the benzylic carbon, so that the significance of calculations that predict that this change in chemical reactivity is accompanied by a net buildup of negative charge at this carbon is unclear and may be worthy of further attention.

(2) The reaction between dimethylamine and the 1-(4-methoxyphenyl)-2,2,2-trifluoroethyl carbocation **5** gives nearly equal yields of the C-α amine adduct and of the diamine product of nucleophilic aromatic substitution at the C-4 ring position, followed by amine addition to the resulting 4-dimethylamino-stabilized

carbocation (Scheme 2).[17] These results show that the electrophilic reactivity of the benzylic and C-4 ring carbons of **5** towards amines is nearly identical. Nucleophilic aromatic substitution reactions of methanol, ethanol,[18] and water[19,20] with the 1-(4-methoxyphenyl)-2,2,2-trifluoroethyl carbocation have also been reported. The product of the latter reaction is the neutral quinone methide **6**, which may also be viewed as a zwitterionic benzylic carbocation stabilized by the strongly electron-donating 4-O⁻ substituent.



Scheme 2



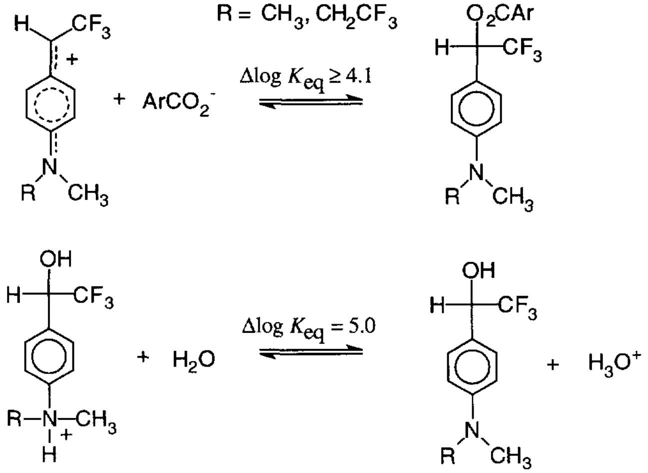
6

(3) The 1-(4-methylthiophenyl)-2,2,2-trifluoroethyl carbocation is reduced to the corresponding alkane by sulfite ion.[21] This result is consistent with addition of sulfite ion to the C-4 ring position, followed by breakdown with loss of neutral SO_3 to form a carbanion, which is then protonated by solvent.

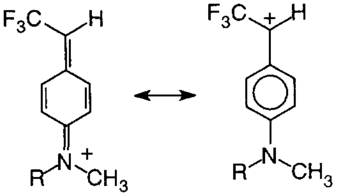
(4) A qualitative estimate of the extent of charge delocalization at **7** has been obtained by comparison of the effect of replacement of an *N*-methyl group by an *N*-trifluoroethyl group on the equilibrium constants for:
(i) addition of 4-nitrobenzoate anion to **7** ($\Delta\log K_{eq} \geq 4.1$, Scheme 3);
(ii) deprotonation of the anilinium ions **8** ($\Delta\log K_{eq} = 5.0$, Scheme 3); and,
(iii) a hypothetical reaction in which there is a unit decrease in localized charge at the benzylic carbon of **7** ($\Delta\log K_{eq} \approx 0.5$).[22] The effect of the *N*-trifluoroethyl substituent on the equilibrium constant for the addition of nucleophiles to **7** is much larger than would be expected if the positive charge were localized on the benzylic carbon: it is more than 80% of the substituent effect for the reference reaction in which a unit charge is lost upon deprotonation of the nitrogen of **8**. These data do not fully describe the distribution of charge between the benzylic and three of the ring carbons of **7**, but they do support the qualitative conclusion that the center of positive charge at **7** lies significantly closer to nitrogen than to the benzylic carbon,

7

8



Scheme 3



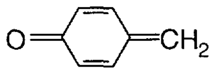
so that these species more closely resemble iminium ions than benzylic carbocations.

It is easy to overlook the consequences of the high degree of charge delocalization at **5-7** and related carbocations because the thermodynamic driving force for their reactions with nucleophiles remains relatively large, the kinetic barriers small and, with a few exceptions noted in the above examples and references, the most reactive electrophilic center of these cations is the benzylic rather than the C-4 ring carbon. The implications of these results are that appreciable π character must develop at the benzylic carbon before the appearance of a reaction barrier, and that this carbon remains more electrophilic than C-4, even after the preponderance of positive charge has shifted to the ring substituent.

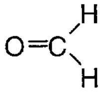
A simple explanation for the preferred addition of nucleophiles to the benzylic rather than to the C-4 ring carbon of highly resonance-stabilized carbocations such as **7** is that the thermodynamic driving force to addition to the former is larger because the aromatic ring is maintained in products. However, this is speculative and the factors that control the regiochemistry of nucleophile addition to highly resonance-stabilized benzylic carbocations deserve further attention.

2.2. Description of the Barrier - Part 1

The extensive work on carbocation-nucleophile combination reactions has produced only limited insight into the origin of the barrier to these reactions and the nature of the electronic interactions between the reactants that produce the barrier. However, chemical intuition suggests that these barriers, which appear only after substantial stabilization of the electrophile by π-electron delocalization, should be modeled as barriers to addition of nucleophiles to a weakly π-bonded electrophilic center. It would follow, then, that part of the difference in the barriers for the addition of nucleophiles to the highly reactive electrophiles **1** and **2** and their relatives **9** and **10** is due to differences in bond strengths in the disrupted π-systems, and that the origin of the small barriers to the reactions of highly unstable carbocations might become apparent from a consideration of the nature of the chemical barriers to reaction of the stable electrophiles **9** and **10** and of how these barriers change as the π-bond is progressively weakened.



9

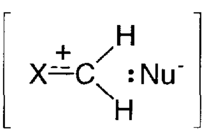


10

The bonding at carbocations stabilized by two or three π-electron-donating substituents (*e.g.*, diarylmethyl and triarylmethyl carbocations) is more complicated than for the monosubstituted carbocations **1-4**, because of difficulties in treating multiple partial π-bonding interactions with the cationic center. However, this should not obscure the empirical relationship between increasing total π-bond order at the cationic center and increasing barrier height for the addition of nucleophiles that is observed upon substitution by multiple π-electron-donating groups.

A description of the barrier to carbocation-nucleophile combination reactions using a valence bond curve crossing model has been reported.[23,24] As originally formulated, this model failed to include valence bond configurations to account for cleavage of a partial π bond at the carbocation, and it is difficult to understand how, without further refinement, it will offer insight into the origin of the reaction barrier.

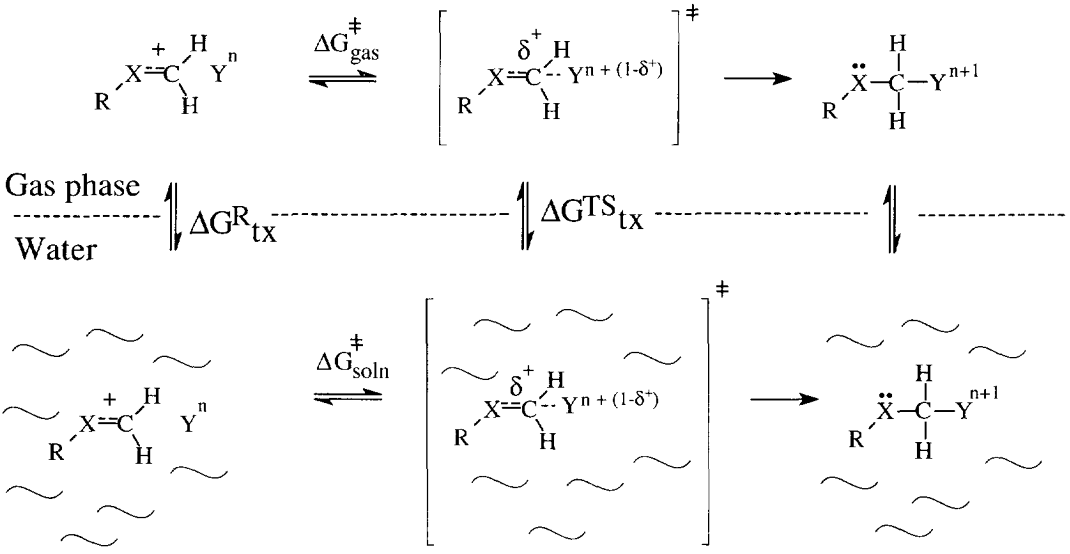
The absence of a kinetic barrier to the addition of nucleophiles to the methyl carbocation shows that the shape of the entire reaction profile is determined essentially by the stabilization gained from formation of a covalent bond. The appearance of a small barrier to the addition of nucleophiles to the resonance-stabilized carbocations **1-4** marks the point at which the magnitude of the destabilizing interactions between the nucleophile and the electrophile exceeds the relatively small stabilization obtained from covalent bond formation during the early stages of the reaction coordinate. The initial unfavorable interactions in this transition state (**11**) would certainly include, and possibly even be dominated by, repulsive electronic interactions that develop as the electron-rich nucleophile approaches the partly-filled π-orbital at the cationic center. Section 3 will present a discussion of how and why the initial small barrier observed for the addition of solvent to **1-4** grows as these carbocations are further stabilized by resonance electron donation.



11

2.3. *Solvent Effects*

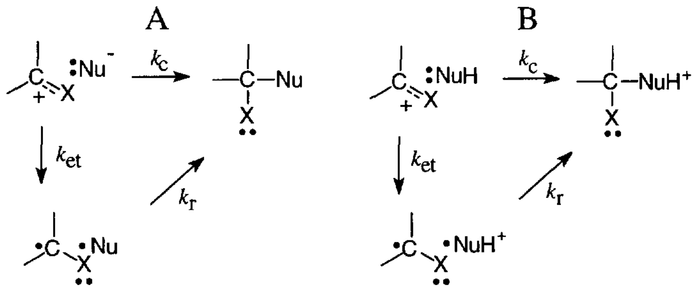
The stabilization of carbocations by interactions with an aqueous solvent is on the order of 50 kcal/mol,[25] and still stronger solvation is expected for nucleophilic anions. Despite the magnitude of these interactions, there is good evidence that they alone do not guarantee the existence of a barrier to carbocation-nucleophile combination. It is not possible to demonstrate rigorously the absence of a significant chemical activation barrier in solution, but for many reactions it would be difficult to argue for its existence. For example, the estimated rate constant for addition of a solvent of 50/50 trifluoroethanol/water to the benzyl carbocation is $k_s \approx 4 \times 10^{11}$ s^{-1}.[9] Azide ion is 10^6-fold more reactive than solvent towards substituted triarylmethyl carbocations,[26-28] so that in water once the benzyl cation and azide ion are properly aligned to react, it is likely that the time for their passage to products will be on the order even of that for a bond vibration ($1/k_{Nu} < 10^{-13}$ s, see Figure 1). Even smaller "barriers" will be observed for the reactions of more unstable secondary or primary aliphatic carbocations with azide ion in aqueous solution. These arguments support the notion that, in some cases, water and other solvents may provide equal stabilization of encounter complexes between weakly resonance-stabilized carbocations and



Scheme 4

nucleophilic reagents and of the transition state for their combination, whose structure is essentially identical to that of reactants ($\Delta G^{R}_{tx} = \Delta G^{TS}_{tx}$, Scheme 4); that is, the barrier to formation of the transition state is essentially unaffected by transfer of the reactants from the gas phase to aqueous solution ($\Delta G^{\ddagger}_{gas} = \Delta G^{\ddagger}_{soln}$, Scheme 4).

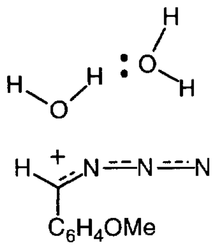
Despite the absence of pertinent experimental or theoretical data, there is no question that the barriers to the nucleophilic addition of anions to carbocations will be substantially larger and much more likely to be observed for reaction in solution than for reaction in the gas phase. The absolute barrier height in the gas phase will be smaller than that in solution because of the enormous difference in the thermodynamic driving force for the condensed and gas phase reactions. Gas phase reactions may even follow a different stepwise pathway involving electron transfer to form a radical pair that then combines (Scheme 5A).[29-31] If the direct nucleophile addition reaction is a viable pathway in the gas phase (k_c, Scheme 5A), then the transition state may show a smaller polar and larger biradical character than that for the reaction in water where polar transition states are effectively stabilized by interactions with solvent (Scheme 4).



Scheme 5

It is important to distinguish between solvent effects on addition reactions of anionic and of neutral nucleophiles to carbocations, because on conversion of reactants to products the two classes of reaction result in decreases and increases, respectively, in absolute charge and solvation at the nucleophilic site (Scheme 5). The values of ΔH for addition of water to the methyl carbocation and of methanol to the ethyl and isopropyl cations in the gas phase determined from thermochemical data are -66, -50, and -33 kcal/mol, respectively.[32] This trend suggests that addition of neutral alcohol nucleophiles will become endothermic with further stabilization of the carbocation by resonance. It would be interesting to determine whether the change from delocalized charge at carbocations such as **1-4**, to oxygen-localized charge at their water adducts (oxonium ions) is *favored* by transfer from the gas phase to water (Scheme 4), or whether the driving forces for addition of neutral nucleophiles are smaller in solution than in the gas phase.

There is both a second-order term, k_B, and a 100-fold larger third-order term, k_T, in the rate equation for the reaction of water with the α-azido-4-methoxybenzyl carbocation in nearly anhydrous acetonitrile ($[H_2O] < 0.001$ M).[12,33] These terms were determined by analysis of the change in the reaction products from mostly (86%) 4-methoxybenzonitrile, which forms in a classic Schmidt rearrangement in the nearly anhydrous solvent, to mostly (> 97%) 4-methoxybenzaldehyde, which forms from the addition of water ($[H_2O] = 0.06$ M) to the α-azido carbocation followed by loss of HN_3 from the α-azidohydrin. A simple explanation for these data is that development of oxygen-localized charge in the transition state for the addition of water to the delocalized α-azido carbocation is unfavorable in the organic solvent acetonitrile, so that this transition state is stabilized by "solvation" by a second water molecule. This may correspond to classical general base catalysis, or to



stabilization of the transition state by hydrogen bonding without formal proton transfer.

Single electron transfer pathways (k_{et}, Scheme 5) and biradical transition states are less likely for the reaction of neutral than of anionic nucleophiles with carbocations in the gas phase, because the thermodynamic driving force for electron transfer between cations and neutrals (positive charge maintained in the radical cation product) will be much smaller than for transfer between cations and anions (both charges destroyed in the radical products); and it may in fact not be feasible if the former electron transfer reaction is unfavorable. I am not aware of experiments or calculations to determine the free energy change for electron transfer between neutral nucleophiles and resonance-stabilized carbocations, but this change could be estimated from the nucleophile ionization potential and the carbocation electron affinity. As with many of the problems discussed in this Report, the dearth of experiments to determine the effect of solvation on the kinetics and thermodynamics for addition of nucleophiles to carbocations limits the discussion of these effects to elementary generalizations and unproven speculation.

3. SUBSTITUENT EFFECTS ON THE BARRIER HEIGHT

3.1. Reaction Coordinate Profiles

Once brought into existence, the height of the barrier to carbocation-nucleophile combination will vary with changes in polar and resonance electron-donating substituents. The variations in barrier height with changing thermodynamic driving force may be modeled by construction of reaction profiles from intersecting potential energy surfaces, which for simplicity are often drawn as simple parabolas (Figure 2). There are many ideas about how best to define progression along the reaction coordinate in Figure 2. This progression may be viewed as the change in bond-order between the nucleophile and the cationic carbon on moving from reactants to products, and it can be estimated empirically as the fractional expression of equilibrium substituent effects on the reaction rates, because this fraction should depend in some way on fractional bond development at the transition state.[34–37] However, the relationship between empirical structure-reactivity parameters and bond formation in the transition state is not well understood. Alternatively, the progress along the reaction coordinate may be described as the transition from a set of valence bond configurations for the reactant to the corresponding set of configurations for the product.[23,24] No attempt is made in this section to compare or judge the effectiveness of these different methods for construction of reaction coordinates, but it is assumed that each should be capable in some way of describing the shapes of the intersecting parabolas that define the coordinate for carbocation-nucleophile combination reactions, and that each should provide a rationalization for the observed increases in intrinsic reaction barrier with increasing resonance stabilization of the carbocation intermediate.

$$\Delta G^{\ddagger} = \Lambda(1 + \Delta G^{o}/4\Lambda)^{2} \tag{1}$$

Reaction profiles for simple and complex reactions have been modeled by the Marcus equation (Eq 1) which expresses the activation energy $\Delta G^{\ddagger}$ as a function of two parameters:[38,39] (1) $\Lambda = \Delta G^{\ddagger}$ when $\Delta G^{o} = 0$; this provides a measure of the intrinsic rate for the reaction using the thermoneutral reaction as a reference point (Λ is also referred to as the intrinsic reaction barrier); and (2) ΔG^{o}, the overall free energy change for the reaction which provides a measure of the displacement of the parabolic energy surfaces from the reference point where

$\Delta G^o = 0$. Figure 2A shows the effect on $\Delta G^\ddagger$ of a change in ΔG^o: this is represented by shifting the relative positions of the parabolic energy surfaces, but leaving their shape unaffected. Figure 2B shows a change in $\Delta G^\ddagger$ caused by an increase in the intrinsic reaction barrier from Λ_1 to Λ_2. This increase in Λ reflects an increase in the curvature of one or both of the intersecting potential energy surfaces.

Figure 2C shows that it is important to separate substituent effects on ΔG^o from effects on the kinetic intrinsic reaction barrier (Λ). A substituent that decreases the thermodynamic driving force for a reaction of constant intrinsic barrier would change the activation barrier from position 1 to 2. However if the change in ΔG^o is accompanied by an increase in the curvature of the energy surface and an increase in Λ, then a higher activation barrier and a more central reaction transition state at position 3 would be observed.

There are at least two limitations to the use of the Marcus equation to describe the changing activation barriers to carbocation-nucleophile combination: (1) The experimental determination of intrinsic reaction barriers Λ for thermoneutral reactions of unstable carbocations such as **1-4** is problematic. Thermoneutrality could be approached by use of weakly nucleophilic reagents, but it is not clear that sufficiently weak nucleophiles exist; or, by the addition of strongly resonance electron-donating substituents, but these will also perturb the intrinsic reaction barrier (see below). (2) The full Marcus equation (not given) also contains a "work term" which is the energy required to move from the free reactants to a complex in which they are properly aligned to react. It is generally difficult to determine the relative contributions of the work term and the intrinsic barrier to the observed reaction barrier. These practical limitations aside, simple Marcus theory *does* provide an informative framework for a qualitative evaluation of the effect of changing the shape (curvature) of the reaction energy surface on rate-equilibrium relationships for these addition reactions in terms of the changes in Λ, a readily identifiable (if not measurable) experimental quantity.

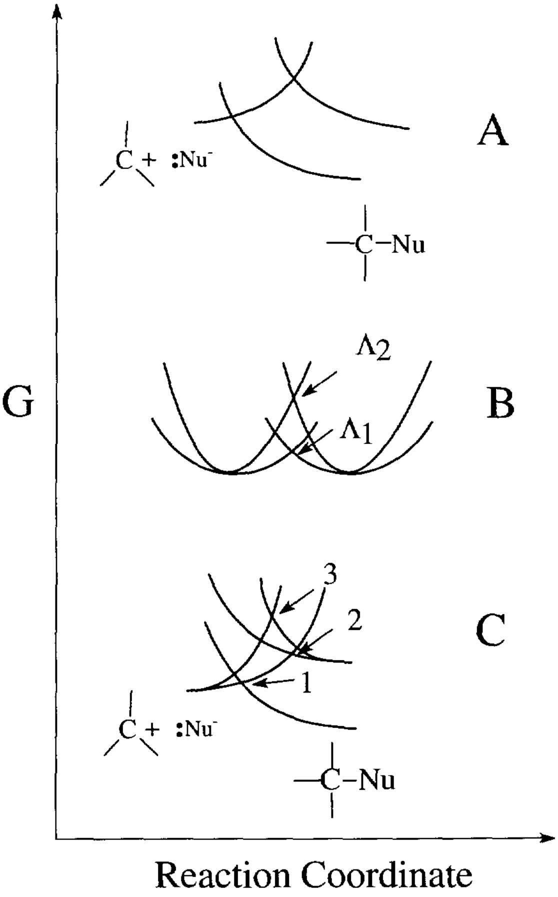


Figure 2. (A) Reaction profiles showing the effect on $\Delta G^\ddagger$ of changing ΔG^o for a constant intrinsic barrier (Λ). (B) Reaction profiles showing the effect of changing Λ for a constant ΔG^o. (C) Reaction profiles showing a comparison of the effects on $\Delta G^\ddagger$ (1) of changing ΔG^o only (2), and of changing both Λ and ΔG^o (3).

3.2. Resonance Effects

There is direct evidence that the intrinsic barriers for protonation of carbanions increase with increasing resonance electron donation from the carbanionic center to electron-withdrawing substituents.[40,49,50] By analogy, the intrinsic barriers to carbocation-nucleophile combination (Figure 2B) are expected to increase with increasing stabilization of the carbocation by electron-donating substituents. The clearest evidence for this effect is the observation of nearly invariant pseudo-first-order rate constants, $k_s \approx 5 \times 10^7$ s^{-1}, for addition of a solvent of 50/50 trifluoroethanol/water to resonance-stabilized 4-methoxybenzyl carbocations as the α-substituent R is varied from strongly electron-donating (*e.g.* MeO)[1] to strongly electron-withdrawing (*e.g.* CF_3[2,19,41,42] or α-CO_2Et[43]) (Figure 3). These changes in α-substituents cause large increases in the thermodynamic driving force for the reaction, but the effects are attenuated by an increase in stabilizing resonance electron donation from the 4-methoxybenzyl ring.[13] The experimental results are illustrated by the reaction coordinates in Figure 3A for addition of water to 4-$MeOC_6H_4CH(R)^+$. The approach to thermoneutral reactions by a change to (hypothetical) progressively weaker nucleophiles is illustrated by Figure 3B. Thermoneutrality will be first attained for reaction of the most stable carbocation (R^1 = OMe), but use of progressively weaker nucleophilic reagents will be required for the observation of thermoneutral addition to the carbocations of intermediate (R^2 = H) and greatest (R^3 = CF_3) instability; and the intrinsic barriers to these reaction will progressively increase (Figure 3B). That is, a relatively small intrinsic barrier is observed for addition of nucleophiles to 4-$MeOC_6H_4CH(OMe)^+$, which is relatively weakly stabilized by resonance electron donation from the 4-methoxyphenyl ring; and a large intrinsic barrier is observed for the reaction of 4-$MeOC_6H_4CH(CF_3)^+$, where the resonance interaction is a maximum for this series. The increases in the intrinsic barrier reflect the increasingly steep curvature of the reaction coordinate profile with increasing stabilization of the carbocation by resonance electron donation from the 4-methoxyphenyl ring (Figure 2B).

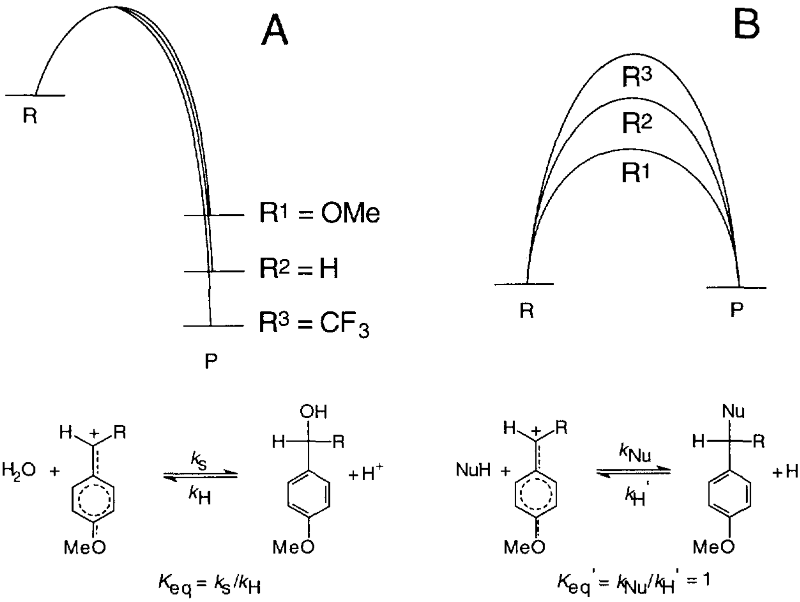


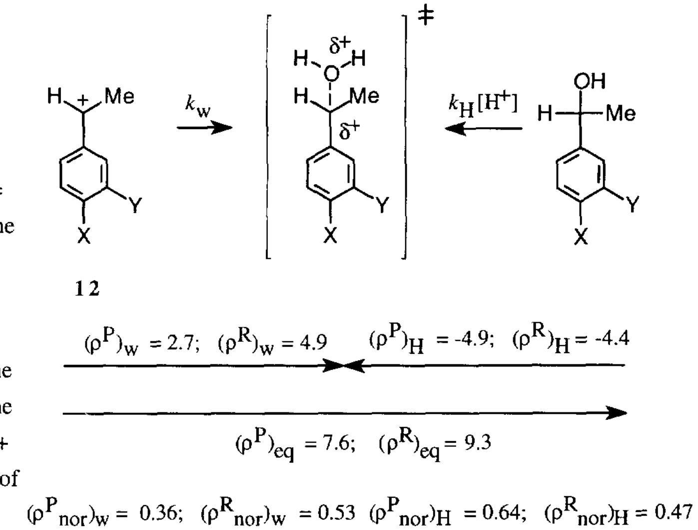
Figure 3. Reaction coordinates that show: (A) the relative kinetic and thermodynamic barriers for addition of water to α-substituted 4-methoxybenzyl carbocations; and (B) the relative intrinsic barriers to thermoneutral addition of hypothetical weakly nucleophilic reagents NuH to these carbocations.

3.3. Polar Effects

Changes in carbocation stability due to simple polar substituent effects are generally treated as displacements in the position of intersecting potential energy surfaces of constant curvature (constant Λ, Figure 2A). However, polar substituents may affect both ΔG^o *and* the intrinsic reaction barrier (Λ) for carbocation-nucleophile combination, if they also significantly perturb stabilization of the carbocation by resonance electron donation. For example, the addition of an α-trifluoromethyl group to the 4-methoxybenzyl carbocation causes a large overall destabilization of the carbocation by a polar effect,[44] but the effect is attenuated by enhanced resonance electron donation from the 4-methoxyphenyl ring (see above). The net result is the increase in the intrinsic barrier described in the preceding section (Figure 3).

3.4. Imbalance and the Principle of Nonperfect Synchronization

The most striking result from studies of rate-equilibrium relationships for the addition of nucleophiles to carbocations is the repeated observation of large differences in the fractional expression of equilibrium polar and resonance substituent effects on reaction rate constants.[10,15,45-47] This is illustrated by the Hammett reaction constants for addition of water to ring-substituted 1-phenylethyl carbocations (Scheme 6).[15] The polar substituent effects were quantified by varying the 3-Y substituent (Y = H, MeO, Br, NO_2) at the 1-(4-methoxyphenyl)ethyl carbocation (**12**, X = MeO). Hammett correlations with slopes of $(\rho^P)_w = 2.7$ and $(\rho^P)_H = -4.9$, respectively, were obtained for the water addition reaction (k_w), and for generation of these carbocations by acid-catalyzed cleavage of the corresponding 1-arylethyl alcohols. The Hammett reaction constant $(\rho^P)_{eq}$ for the equilibrium addition of water is $(\rho^P)_w + [-(\rho^P)_H] = 7.6$. Analysis of the effects of resonance electron-donating 4-X substituents (X = Me_2N, MeO, MeS, PhO, Me) gave $(\rho^R)_w = 4.9$, $(\rho^R)_H = -4.4$ and $(\rho^R)_{eq} = 9.3$ for the resonance reaction constants. Normalized Hammett constants (ρ_{nor}) were calculated as the fraction of the equilibrium substituent effects expressed in the rate constants; *e.g.*, $(\rho^P{}_{nor})_w = (\rho^P)_w/(\rho^P)_{eq} = 2.7/7.6 = 0.36$.[45,48] The difference in the fractional expression of resonance and polar substituent effects in the transition state is striking: only 36% of the polar effect of 3-Y substituents on K_{eq} for conversion of reactants to products is expressed in k_w for water addition, which suggests that the transition state lies significantly closer to reactants than to products, while a much larger fraction (53%) of the effect of resonance electron-donating 4-substituents is expressed in k_w, which is consistent with a more central transition state. Protonated 1-arylethyl alcohols are probable intermediates of addition of water to **12**. Correction of the normalized Hammett reaction

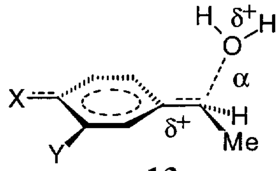


Scheme 6

constants (ρ_{nor}) for polar substituent effects on the equilibrium constants for deprotonation of these putative intermediates ($\rho^P = 1.1$, $\rho^R = 0$) reduces the overall imbalance slightly.[15,45]

The difference in the fractional expression of resonance and polar substituent effects implies a lack of synchronization in their development and has been referred to as the *Principle of Nonperfect Synchronization.*[49,50] These substituent effects are also widely observed for reactions of resonance-stabilized carbanions,[40,49,50] where they are manifested as the nitroalkane anomaly.[51,52]

A large body of data suggest that imbalances in the transition-state expression of equilibrium polar and resonance substituent effects are common for organic reactions in solution, and a recent computational study is consistent with their existence for thermoneutral proton transfer between acetaldehyde and its enolate ion in the gas phase.[53] With this one exception, I am not aware of a treatment of these imbalances at a level that would satisfy theoretical and computational chemists that they are indeed real phenomena; however, the following qualitative explanations may serve as a point of departure for further theoretical treatments.



13

(1) Kresge has proposed that imbalances exist because of the larger change in resonance than in polar interactions between substituents and the reaction center with increasing covalency at this center.[52] This proposal is illustrated by the hypothetical transition state **13** for addition of water to ring-substituted 1-phenylethyl carbocations, where α is the fractional development of a covalent bond between the nucleophile and the benzylic carbon. The change in inductive interactions between the 3-substituent and the cationic center will be some function of α; but, the falloff in resonance interactions with 4-substituents will depend on both the progress towards covalent bond formation (α), and on the extent to which movement from planar to pyramidal geometry further inhibits electron delocalization to the now partly-filled and rehybridized benzylic π-orbital. That is, the maximum fraction of the equilibrium resonance effect that can be expressed in a transition state with a fractional bond order α to water is 1 - α, but only part of this will be observed because the stabilizing electronic overlap is reduced by the change to a more pyramidal geometry of the benzylic carbon. Assuming that $(\rho^P_{nor})_w = 0.36$ for the addition of water (Scheme 6) corresponds to 36% bond formation, and that there is a further 36% reduction in the fractional expression of the resonance substituent effect expected for a balanced transition state, then $(\rho^R_{nor})_w = 1 - (0.64)^2 = 0.59$, which is close to the observed value of $(\rho^R_{nor})_w = 0.53$.

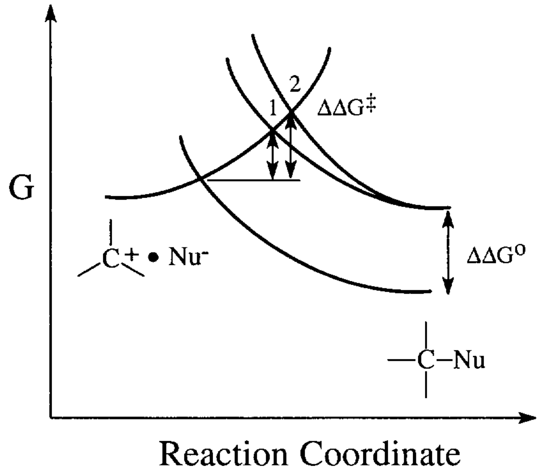


Figure 4. Comparison of the change in activation barrier (ΔΔG‡) for a polar substituent which affects only ΔG° (1) and for a resonance electron-donating substituent which affects both ΔG° and the intrinsic reaction barrier Λ (2).

(2) Imbalances in the transition state expression of equilibrium inductive and resonance substituent effects are a direct consequence of the increasingly sharp curvature along the reaction coordinate (increasing intrinsic reaction barrier) observed on moving from weakly to strongly resonance-stabilized carbocations.

This is illustrated in Figure 4, where $(\Delta\Delta G^{\ddagger})^1/\Delta\Delta G^o$ is the fractional expression of the effect of a polar electron-donating substituent that changes the thermodynamic driving force for the reaction but *not* the overall shape of the reaction profile, and $(\Delta\Delta G^{\ddagger})^2/\Delta\Delta G^o$ is the larger factional expression of the effect of a resonance electron-donating substituent that affects both the thermodynamic driving force *and* the intrinsic reaction barrier. Bernasconi has described a graphical analysis of rate-equilibrium data which shows that if there are different Brønsted or normalized Hammett reaction constants for polar and resonance effects on rate constants for a reaction, then there will be a resonance substituent effect on the intrinsic reaction barrier.[40]

Strongly electron-withdrawing α-substituents destabilize the 4-methoxybenzyl carbocation by a polar substituent effect and also increase the intrinsic barrier to the addition of nucleophiles to the carbocation, because of an accompanying increase in resonance electron donation from the 4-methoxyphenyl ring to the benzylic carbon (Section 3.2, 3.3 and Figure 3). An imbalance in the expression of these opposing polar and resonance effects provides a semiquantitative explanation for the nearly invariant rate constants k_s (s^{-1}) for the addition of a solvent of 50/50 trifluoroethanol/water to α-substituted 4-methoxybenzyl carbocations (Section 3.2).[2] Figure 5 illustrates the situation for the substitution of an α-CF_3 for the α-CH_3 group at $4\text{-}MeOC_6H_4CH(CH_3)^+$, where the polar effect ($\Delta\Delta G^o{}_P$) is the destabilization of the parent cation to create a hypothetical species with the same extent of electron delocalization from the 4-methoxyphenyl ring, and the resonance effect ($\Delta\Delta G^o{}_R$) is the stabilization gained by increased electron delocalization in the α-CF_3-substituted carbocation, and the observed effect ($\Delta\Delta G^o{}_{obsd}$) is the difference between these polar and resonance effects. The addition of solvent to the two carbocations occurs with the same rate constant, $k_s = 5 \times 10^7\ s^{-1}$, so that $\Delta\Delta G^{\ddagger} = 0$.[41,42] This curious result may be due to an imbalance in the expression of destabilizing inductive and stabilizing resonance interactions in the transition state. That is, this imbalance would lead to the cancellation of the two effects if the difference between the fractional expression of the large polar effect $\Delta\Delta G^o{}_P$ and the small resonance effect $\Delta\Delta G^o{}_R$ at the transition state for the addition of solvent were sufficiently large [$(\rho^R{}_{nor})_s > (\rho^P{}_{nor})_s$, Eq 2].

$$\Delta\Delta G^{\ddagger} = (\rho^P{}_{nor})_s\Delta\Delta G^o{}_P + (\rho^R{}_{nor})_s\Delta\Delta G^o{}_R \approx 0 \tag{2}$$

Resonance attenuation ($\Delta\Delta G^o{}_R$) of the polar effect of the α-CF_3 group on the stability of the hypothetical cation at the top of Figure 5 cannot be evaluated by experiment. However, this attenuation is a real effect that increases the electrophilic reactivity of the C-4 ring carbon relative to that of the benzylic carbon, so that these two centers show similar reactivities towards amine nucleophiles (Section 2.1).[17] The large difference between the effect of a 4-methoxy substituent on k_{solv} for solvolysis of 1-phenylethyl chloride (6×10^4)-fold[54] and 1-phenyl-2,2,2-trifluoroethyl tosylate (4×10^7)-fold[44] shows that the 4-methoxy group stabilizes the transition state for these reactions by 6.5 kcal/mol and 10.3 kcal/mol, respectively. The difference corresponds to a 3.8 kcal/mol greater stabilization by the 4-methoxy group of the cationic transition state for solvolysis of 1-phenyl-2,2,2-trifluoroethyl tosylate, due to enhanced resonance interactions between the developing cationic center and the 4-methoxyphenyl ring. There is no a direct relationship between this effect of 3.8 kcal/mol and the magnitude of $\Delta\Delta G^o{}_R$ in Figure 5. However these data provide qualitative support for the proposal of a large attenuation of the destabilizing polar effect of the α-CF_3 substituent by a stabilizing resonance effect.

Electron-donating and electron-withdrawing α-substituents cause normal decreases and increases, respectively, in k_s (s^{-1}) for reaction of the 4-methylbenzyl carbocation with aqueous trifluoroethanol.[2] Here, the polar effects of α-substituents ($\Delta\Delta G^{o}_{P}$, Figure 5 and Eq 2) dominate the attenuating resonance effect of the 4-methylphenyl ring ($\Delta\Delta G^{o}_{R}$), which is smaller than the attenuation by the 4-methoxybenzyl ring because of weaker electron donation from the 4-Me than from the 4-MeO substituent.

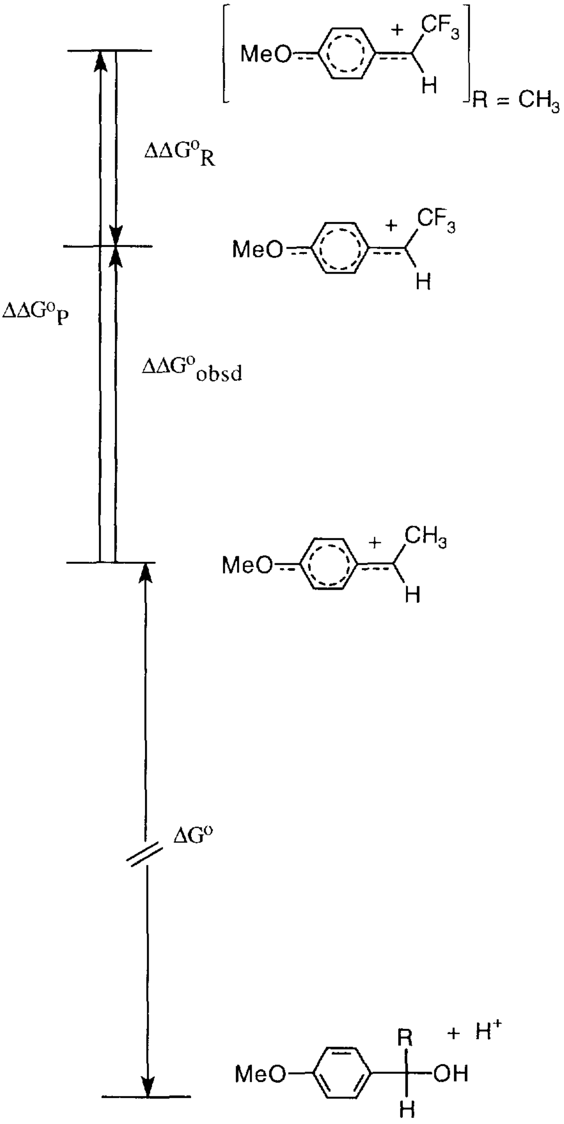


Figure 5. Separation of the observed effect of an α-CF_3 for α-CH_3 substitution on carbocation stability ($\Delta\Delta G^{o}_{obsd}$) into polar ($\Delta\Delta G^{o}_{P}$) and resonance ($\Delta\Delta G^{o}_{R}$) substituent effects.

Concluding Remarks. Rate-equilibrium relationships for polar and resonance substituent effects on the formation and reaction of carbocations and carbanions show that resonance interactions are invariably expressed to a smaller extent in the transition states for their formation (where there is a relatively small development of the resonance interaction), and to a larger extent in the transition states for their reaction (where there is a relatively large loss of the resonance interaction), than are polar interactions. This phenomenon has been observed in several different laboratories, and while there is no serious controversy about its origin, differences in the representation of the effect may obscure the issue of its origin.

This author prefers to view these imbalances as resulting directly from the sharper changes in the curvature of the reaction coordinate profile caused by resonance effects than by inductive effects (Figure 4). This explanation is relatively easy to understand, it does not raise the question of the utility of structure-reactivity parameters as probes for the structure of the reaction transition state, and it focuses attention on understanding the explanation for the differences in resonance and inductive substituent effects on intrinsic reaction barriers (Figure 4), because these differences lead directly to the observed imbalances and may be viewed as the underlying cause for these effects.

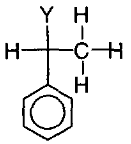
Kresge's semiquantitative explanation for a difference in the fractional expression of resonance and inductive effects at the transition state for reaction of resonance-stabilized reactive intermediates (see **13**)[52] has been especially valuable, because in the absence of a more rigorous explanation for the origin of these imbalances it compels one to conclude that they are indeed real and reasonable effects.

Imbalances in the expression of polar and resonance effects at a transition state may be considered to arise from their different "rates" of development on moving from reactants to transition state. For example, the larger fractional expression of resonance than of polar effects in the transition state for addition of nucleophiles to carbocations shows that, compared with polar interactions, resonance interactions develop relatively slowly, and are lost relatively rapidly, when the transition state is approached from the neutral substrate and from the carbocation, respectively.[40,49,50] Changes in polar and resonance interactions between substituents and the reaction center on movement to the transition state have been separated by assuming that polar interactions develop synchronously with the formation of a covalent bond to the carbocation, that resonance interactions develop with the electronic reorganization that accompanies the change from sp^2 to sp^3 hybridization at carbon, and that these processes may be assigned separate coordinates on a two-dimensional reaction coordinate profile.[35] Nonsynchronization in the development of polar and resonance interactions may be conveniently represented on these diagrams. However, such diagrams suffer from difficulties in scaling of the normalized structure-reactivity parameter for resonance substituent effects to the changes in hybridization at the reacting carbon. For example, a 50% loss of a ground-state carbocation-stabilizing resonance effect in the transition state for addition of a nucleophile probably *does not* signify a 50% change in the hybridization (whatever that might mean) at the reacting carbon, but rather a smaller change in hybridization (*e.g.*, 30%) which causes a larger fractional falloff in resonance delocalization because the changes in geometry inhibit the resonance interaction at the partly rehybridized carbon (*i.e.*, only 70% of the expected 70% resonance interaction is observed, Section 3.4). Therefore, it is important to remember when using these reaction coordinate diagrams that nonsynchronization of the expression of resonance and inductive substituent effects may not in fact correspond to nonsynchronization of covalent bond formation to, and changes in the hybridization of, the reacting carbon.

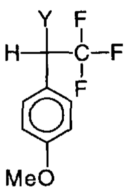
3.5. Ground State Effects

Substituent effects on kinetic and thermodynamic barriers to formation and reaction of carbocations are usually dominated by interactions between the substituent and the cationic center. However, substituent effects on ground state stability are often significant, and neglect of these may lead to confusion or erroneous conclusions about substituent effects on carbocation stability.

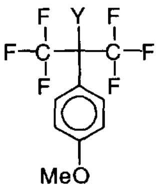
14-Y



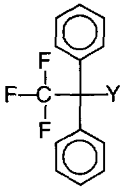
15-Y



16-Y



17-Y

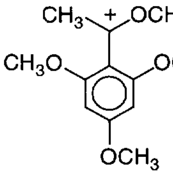


	14-Y	15-Y	16-Y	17-Y
$k_{\mathrm{Tos}}/k_{\mathrm{Br}}$	360	140	9×10^4	1.6×10^6

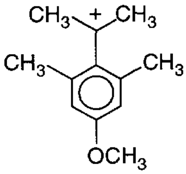
Steric Effects. The most easily recognized ground state effect is destabilization by steric strain that is released in the transition state for formation of a carbocation intermediate. Steric effects on S_N1 solvolyses have been summarized in a recent review.[55] The effects of ground-state strain at uncongested aliphatic centers are small, but they rise sharply with increased crowding. This is illustrated by the increase in the relative rate constants for solvolysis of tosylates and bromides, k_{Tos}/k_{Br}, as the reaction center is changed from a relatively uncongested aliphatic carbon, where there is little or no difference in the crowding of leaving groups of different bulk (*e.g.*, **14-Y**[56] and **15-Y**[42]) to a highly congested center (**16-Y**[19] and **17-Y**[57]). These data are consistent with increasing differences in ground-state strain in substrates with leaving groups of different bulk, which favors ionization of the tosylates (increasing k_{Tos}/k_{Br}) due to the larger relief of strain energy in the transition state for departure of the more bulky nucleofuge.

Ground-state steric effects make it difficult to evaluate the polar/resonance effects of the second α-CF_3 group on the stability of $4\text{-}MeOC_6H_4C(CF_3)_2^+$. The effect on k_{solv} of substitution of an α-CF_3 for the α-H at **15-OTs** to give **16-OTs** is only 2.6-fold, which shows that polar/resonance and steric effects of the second α-CF_3 group roughly cancel, but it is 1700-fold for the same substitution at **15-Br** to give **16-Br**, where a reduction in the size of the leaving group allows the polar/electronic effects of the trifluoromethyl group to dominate.[19] It is also difficult to distinguish ground-state destabilization by strain from destabilization by electronic interactions between electronegative groups. For example, **17-OTs** may be destabilized relative to **17-Br** either by steric interactions or by dipole-dipole interactions between the nucleofuge and the α-CF_3 group which may be larger for the more electronegative oxygen leaving group.

Steric effects on barrier heights to carbocation-nucleophile combination reactions will be observed when there is an increase in steric strain on moving to the transition state. The addition of one α-CF_3 group to the 4-methoxybenzyl carbocation to give $4\text{-}MeOC_6H_4CH(CF_3)^+$ creates, at best, a small steric barrier to addition of solvent, but a second α-CF_3 group causes a 10-fold reduction in k_s for the addition of aqueous trifluoroethanol, from 5×10^7 to $5 \times 10^6\ s^{-1}$.[19] The simplest explanation for this effect is that there is partial expression of the steric/electronic strain in the product at the transition state for the nucleophilic addition. There is good evidence that the pair of *ortho*-methoxy groups at **18**[58] and the *ortho*-methyl groups at **19**[59] provide steric hindrance to reaction of these carbenium ions with solvent as a Lewis base; instead solvent reacts as a Brønsted base at the more accessible α-methyl group(s) to form the corresponding α-substituted styrenes.



18



19

Electronic Geminal Effects. There is extensive evidence from thermochemical measurements,[60] *ab initio* calculations,[61,62] and experiment[63,64] that geminal interactions between electronegative substituents are stabilizing. For example, the geminal hydroxyl groups at formaldehyde hydrate are 17.4 kcal/mol more stable than isolated hydroxyl groups at methanol.[61] Such stabilizing interactions are strongest between good first-row π-electron donors and σ-electron acceptors. They decrease with changes in the relative π-donating and σ-accepting strength of the interacting first-row elements, and fall off very sharply to become, eventually, a destabilizing interaction on progression to higher row elements. The interaction is destabilizing if the substituents are both σ-donors or both π-donors.[65]

$$HOCH_3 + HOCH_3 \overset{\Delta G^o}{\rightleftharpoons} CH_4 + HOCH_2OH$$

$$\Delta G^o = -17.4\ \text{kcal/mol}$$

Geminal interactions between the nucleofuge and substituents at aliphatic carbon may severely complicate the evaluation of the effects of α-heteroatoms on rate and equilibrium constants for formation of carbocations (where these interactions are lost) when the magnitude of the geminal interaction varies for different pairs of α-heteroatoms. The 5-fold larger rate constant for solvolysis of 4-methoxybenzyl fluoride than of methoxymethyl fluoride in water (Figure 6) provides evidence that a 4-methoxybenzyl group is marginally more effective at stabilizing the methyl carbocation than is a methoxy group. But, the 10^4-fold larger rate constant for solvolysis of methoxymethyl chloride than of 4-methoxybenzyl chloride in water is consistent with the opposite conclusion (Figure 6).[66] These comparisons do not lend themselves to simple conclusions about substituent effects on carbocation stability, because for methoxymethyl derivatives the ground-state is stabilized by geminal interactions between the α–methoxy group and the electronegative leaving group, and these interactions differ for different nucleofuges.[61]

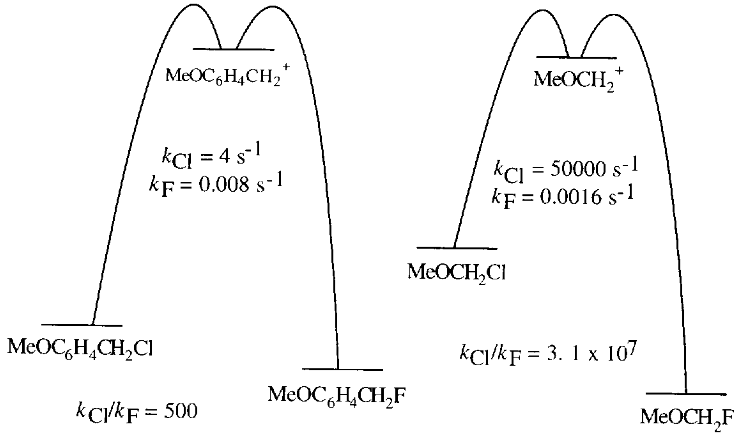
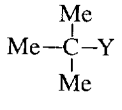


Figure 6. Hypothetical reaction coordinates for solvolysis of 4-methoxybenzyl and methoxymethyl derivatives in water.[66] The relative ground-state stabilities are drawn to scale and are calculated from the rate constants for $D_N + A_N$ solvolysis assuming identical rate constants for addition of the nucleophilic anions to the respective carbocation intermediates. This assumption is unlikely to be entirely valid, but its failure will not affect the conclusions given in the text, because the methoxymethyl and 4-methoxybenzyl carbocations are both highly reactive species, and they will have small selectivities, and even smaller *differences* in selectivity, towards nucleophiles.

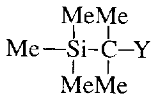
For 4-methoxybenzyl derivatives, the phenyl ring effectively insulates the 4-methoxy group from electronic interactions with the leaving group,[67] so that the 60,000-fold larger value of k_{Cl}/k_F for reaction of $MeOCH_2X$ than of $4\text{-}MeOC_6H_4CH_2X$ can be explained by a ≈ 6.4 kcal stronger geminal ground-state stabilization of $MeOCH_2F$ than of $MeOCH_2Cl$ (Figure 6). The difference in the geminal stabilization of $HOCH_2F$ and $HOCH_2Cl$ obtained from *ab initio* calculations, 10.4 kcal/mol, is even larger than the estimated 6.4 kcal/mol stabilization of $MeOCH_2F$ towards solvolysis.[66]

The variations in the rate constant ratios for solvolysis of **20-Y** and **21-Y** with changing leaving group Y (Table 1) illustrate the difficulty in estimating the relative effects of α-silyl and α-carbon substituents on carbocation stability from rate constants for $D_N + A_N$ (S_N1)[68] solvolysis.[69] These results are in excellent agreement with high-level *ab initio* calculations which show that a geminal silicon-oxygen interaction is *destabilizing* relative to a carbon-oxygen interaction, and that the difference between geminal interactions with silicon and with carbon becomes progressively smaller on moving from oxygen to chlorine to bromine nucleofuges.[69] The net effect of these

Table 1


$Me_3C\text{-}Y$

20-Y


$Me_3Si\text{-}CMe_2\text{-}Y$

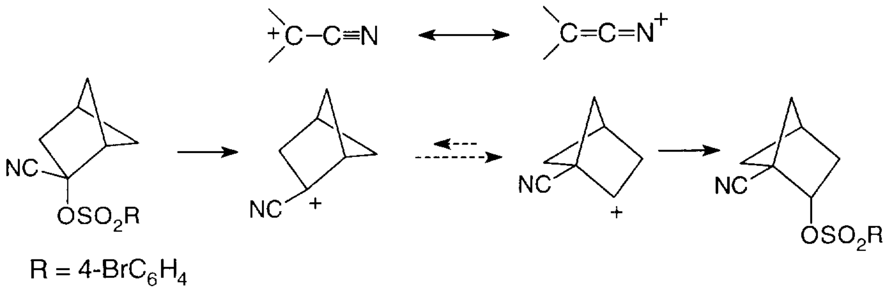
21-Y

Y	$k(Me)/k(Me_3Si)$
$PhCO_2$	3
Cl	792
Br	3010

changes in leaving group is to stabilize **21-Y** relative to **20-Y**, so that the former compound ionizes relatively more slowly which results in an increase in the rate constant ratio $k(\mathrm{Me})/k(\mathrm{Me_3Si})$ for ionization (Table 1).

The complexities of the evaluation of α-substituent effects on carbocation stability are illustrated by studies on α-cyano substituent effects. The observation that replacement of an α-cyano for hydrogen retards solvolysis by 10^3 - 10^4-fold,[70,71] but that the same substitution at the more distant β-position causes an even larger retardation of 10^5 - 10^7-fold is consistent with stabilization of α-cyano carbocations by electron donation from the cyano group (Scheme 7).[71,72] This conclusion was confirmed by ^{13}C and ^{15}N NMR,[73,74] and by computational studies,[75] which revealed partial nitrenium ion character for α-cyano-substituted carbocations.

By contrast, the observation of smooth isomerization of an α-cyano to give a β-cyano substituted brosylate by a cationic mechanism (Scheme 7)[76] suggests that the interaction between the α-cyano group and the cationic center is more destabilizing than that for the β-cyano group. The estimated attenuation of the α-cyano substituent effect from shifting this group to the β-position is 2-3 kcal/mol.[76] Now, if the α-cyano group interacts with the charged center *only* by an inductive effect, then this interaction would be *ca.* 4 - 5 kcal mole, assuming a 2.5-fold attenuation factor[60] for the α-β shift. This is a small effect for a strongly electron-withdrawing group, so that it is likely much of the polar effect of the α-cyano group is offset by a resonance substituent effect (Scheme 7), as shown by the results of NMR[73,74] and computational[75] studies. Finally, geminal interactions between α-cyano and electronegative groups are destabilizing,[65] and this effect is at least partly responsible for the observation of more favorable ionization of α-cyano than of β-cyano-substituted derivatives to form carbocations. Examined as a whole these data show that, relative to a β-cyano group, an α-cyano group destabilizes both cationic reaction intermediates *and* the neutral substrates from which they are formed, that the former effect on carbocation stability is attenuated by resonance, and that the latter effect on the neutral substrate is dominant so that α–cyano-substituted carbocations form more readily in solvolysis reactions.



Scheme 7

In conclusion, care must be exercised in the choice of leaving group when evaluating the effects of α-heteroatoms on carbocation stability from their effects on solvolysis rate constants. The use of leaving groups from the second and higher rows of the periodic table (*e.g.*, $\mathrm{Br^-}$, $\mathrm{I^-}$) is to be preferred to the use of oxygen nucleofuges, which exhibit strong and variable geminal interactions. Electronic geminal interactions with hydrogen are taken as the zero reference point in determination of geminal interactions between other groups.[61,62] Following this convention, substituent effects on carbocation stability, free of contributions of geminal interactions with leaving group, should be determined by measurement or calculation of the thermodynamic barrier to formation of carbocations from neutral alkanes.

Geminal ground-state interactions are easily detected as effects on rate constants for $D_N + A_N$ solvolyses, because these interactions weaken (are lost) on progression to the transition state for heterolytic reactions. These same interactions *develop* at the transition state for carbocation-nucleophile combination and might also affect their barriers. This will depend upon the progress in the transition state towards covalent bond formation to the nucleophile, and the efficiency of expression of electronic geminal interactions across a partial covalent bond. It is not known if these effects are large; however, even a small differential expression of geminal interactions might be significant if it corresponds to a substantial fraction of a small barrier height (see Section 3.6).

Resonance Effects. There is good evidence that dehydration of arene hydrates proceeds by a stepwise mechanism with rate-determining formation of arenium ion intermediates.[77,78a] The decreasing rate constants for specific-acid-catalyzed elimination of water with increasing benzoannulation (Chart 1) are at first glance surprising, because benzoannulation should enhance stabilizing resonance electron donation in the arenium ion-like transition state. The decreases in these solvolysis rate constants require that benzoannulation provide an even greater stabilization of the neutral reactants than of the polar transition state. These data suggest that electron delocalization from the additional aromatic ring(s) towards the cationic center reduces the total aromatic stabilization of the reactive intermediates relative to the stabilization of the neutral reactants by the unperturbed (4n + 2)π Hückel systems. This effect might also represent ground-state stabilization of the substrate by interaction between the hydroxyl group and the benzoannulated ring(s).

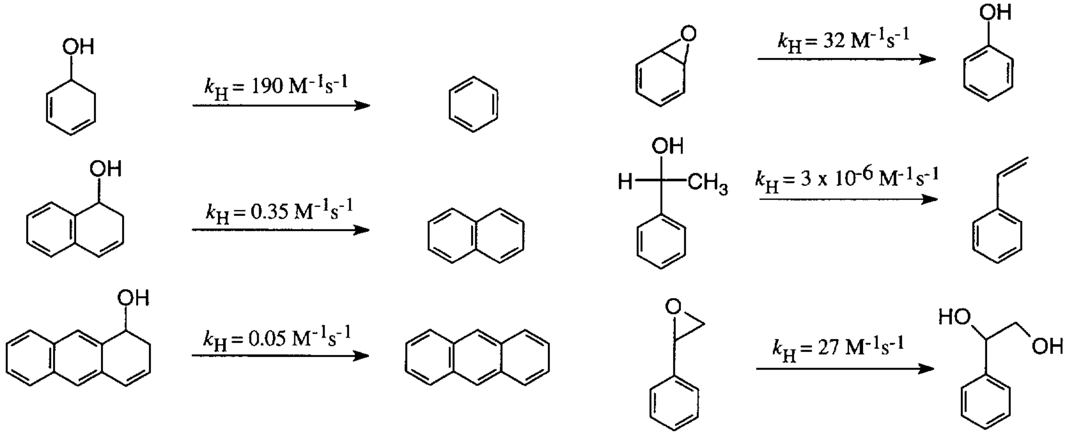
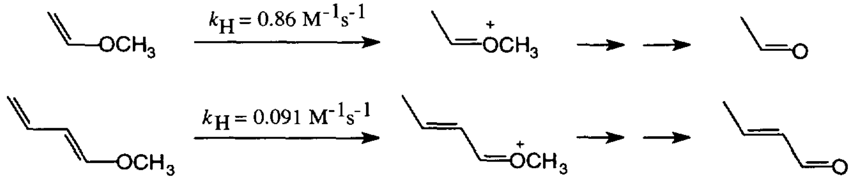


Chart 1

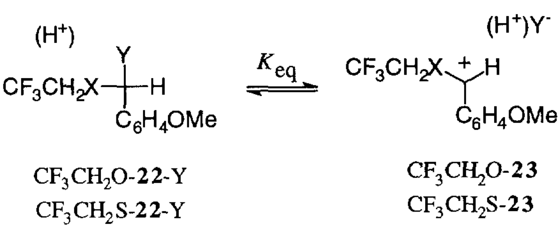
The large difference in the rate constants for specific-acid-catalyzed solvolysis of 1-phenylethyl alcohol ($k_H = 3 \times 10^{-6}\ M^{-1}\ s^{-1}$) and styrene oxide ($k_H = 27\ M^{-1}\ s^{-1}$) (Chart 1) through respective 1-phenylethyl carbocation intermediates is expected because of the large release of epoxide ring strain in the transition state for solvolysis of the epoxide. By contrast, the slightly larger rate constant for aromatization of benzene hydrate ($k_H = 190\ M^{-1}\ s^{-1}$) than of strained benzene oxide ($k_H = 32\ M^{-1}\ s^{-1}$) is surprising. The unexpected low reactivity of benzene oxide is consistent with ground state stabilization by a homoaromatic interaction between the fused rings, which is lost in the transition state for the epoxide-cleavage reaction;[78a] and/or with a relatively small relief of ring strain at an early transition state for cleavage of the epoxide ring of benzene oxide.

A *trans* vinyl substituent causes an 8-fold decrease in the reactivity of methyl vinyl ether in acid-catalyzed hydrolysis.[78b] This result is unexpected, because the vinyl substituent should stabilize the oxocarbenium-like transition state for protonation of the vinyl ether by increasing the delocalization of positive charge. These results suggest that the stabilizing interaction of the vinyl group with the unperturbed carbon-carbon double bond of the reactant is stronger than its interaction with the relatively weak π–bond to oxygen in the oxocarbenium ion intermediate.



3.6. α-Oxygen and α-Sulfur Substituent Effects

A comparison of the rate and equilibrium constants for reaction of α-oxygen- and α-sulfur-stabilized 4-methoxybenzyl carbocations with aqueous trifluoroethanol illustrates our lack of understanding of the origins of these barriers, and they present an interesting challenge to develop qualitative and quantitative models to explain the experimental results.



Scheme 8

Nearly identical equilibrium constants (K_{eq}) are observed for generation of CF_3CH_2O-**23** and CF_3CH_2S-**23** by uncatalyzed solvolysis of the respective α-azido ethers CF_3CH_2X-**22**-N_3 (Scheme 8, Y = N_3). However, K_{eq} for formation of CF_3CH_2S-**23** by acid-catalyzed cleavage of CF_3CH_2S-**22**-OCH_2CF_3 is 23-fold more favorable than formation of CF_3CH_2O-**23** from CF_3CH_2O-**22**-OCH_2CF_3 (Scheme 8, Y = OCH_2CF_3). These data provide another example of ground-state effects on equilibrium constants for carbocation formation. It is more difficult to generate the α-oxygen-stabilized carbocation than the α-sulfur-stabilized carbocation from the respective O,O- and O,S-acetals than from the O- and S-substituted α-azido ethers because there is a larger difference between the strongly stabilizing O,O and weaker O,S geminal interactions in the acetals than between the corresponding geminal interactions in the α-azido ethers.[11]

Figure 7 shows reaction coordinates for the acid-catalyzed formation of CF_3CH_2O-**23** and CF_3CH_2S-**23** from the respective trifluoroethoxide ion adducts (acetals).[11] Relative to the neutral trifluoroethoxide ion adducts, the α-S substituted carbocation is 1.8 kcal/mol more stable than the α-O substituted carbocation (see above), but there is a much larger kinetic barrier both to its formation, $(k_H)_O/(k_H)_S = 40$, and its reaction, $(k_{TFE})_O/(k_{TFE})_S = 900$. These data resolve a longstanding contradiction between the results of gas phase[79] and theoretical studies,[14] which show that an α-S is slightly more effective than an α-O at providing stabilization of carbocations, and the observation of more rapid formation of α-O- than of α-S-stabilized carbocations in solution,[80,81] which suggests the opposite order of substituent effects. In fact, the absolute stabilities of α-O-and α-S-stabilized carbocations are similar, but α-O-stabilized carbocations are formed more rapidly in solvolyses reactions and also react more rapidly with nucleophilic solvent than do α-S-stabilized carbocations (Figure 7). In this case, attempts to infer the relative effects of these α-heteroatoms on carbocation stability from their effects on rate constants for solvolysis led to erroneous conclusions. These results serve as a warning that it is important constantly to test and evaluate assumed rate-equilibrium relationships for carbocation-nucleophile addition reactions.

The structure-reactivity effects illustrated in Figure 7 have been reported by other laboratories. For example, substitution of an α-sulfur for the α-oxygen at the α-methoxy-di(4-methoxyphenyl)methyl carbocation (**24**)[82] causes a 5000-fold decrease in k_s for its capture by water. Similarly, the substitution of a pair of α-sulfur atoms for the α-oxygens at the 2-(4-methoxyphenyl)-1,3-dioxolenium ion (**25**, X = O) has a relatively small effect on the stability of the carbocation relative to the water adduct, but causes large increases in the kinetic barriers to formation and cleavage of the water adduct.[83]

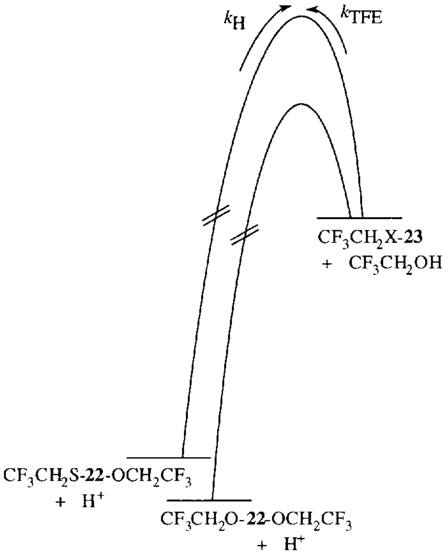
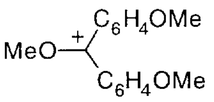
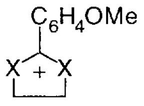


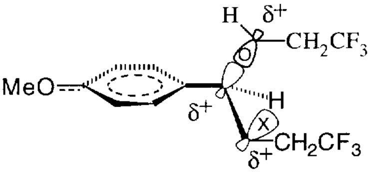
Figure 7. Reaction coordinates for formation of α-O- and α-S-stabilized carbocations from the respective trifluoroethoxide ion adducts, constructed using data from reference 11.



24



25



26

The most important but poorly understood result from our studies of α-O- and α-S-stabilized carbocations is the observation of very different kinetic barriers to the formation and reaction of carbocations of similar thermodynamic stabilities (Figure 7). Two possible explanations have been suggested to account for these differences.[11]

(1) The O,O geminal interactions in the acetal product of reaction of the α-O-stabilized carbocation are stronger than the O,S geminal interactions in the thioacetal product obtained from the α–S-stabilized cation.[14,61] Therefore, part or all of the difference in the barriers to the formation and reaction of these two carbocations might be due to the greater stabilization of the transition state for reaction of the α-O stabilized carbocation by partly-developed electronic geminal interactions between the α-oxygen and the oxygen nucleophile (Section 3.5).

(2) The difference in the kinetic barriers might reflect the greater stabilization of the cationic center by resonance electron donation from α-oxygen than from α-sulfur at the partly sp^3-hybridized benzylic carbon in the transition state (**26**). There is a greater *s*- and less *p*-character for nonbonding electrons and larger *p*- and reduced *s*-character for bonding electrons at sp^3-hybrid orbitals of sulfur than for the corresponding orbitals at oxygen.[84a] Such deviations from sp^3-hybridization are responsible for the small H-X-H bond angle (*ca.* 90°) for H_2S, because there is relatively high *p*-character for the bonding electrons and low *p*-character for the

nonbonding electrons. By contrast, a more normal H-X-H bond angle (*ca.* 104°) is observed for H_2O.[84a] The difference in hybridization for the "sp^3-type" hybrid orbitals that develop on addition of a nucleophile to α-O- and α-S-stabilized carbocations would be expected to lead to a greater falloff in stabilizing π-electron donation from sulfur than from oxygen, because the rehybridizing nonbonding electrons at sulfur would have greater *s*-character and participate more weakly in π-bonding interactions than the corresponding electrons of oxygen. This proposal is supported by results of *ab initio* calculations, which show a 16 kcal/mol smaller barrier to $MeX\text{-}C^+$ bond rotation for the methoxymethyl than for the methylthiomethyl carbocation.[14] This difference in rotational barriers is consistent with more favorable π-electron donation from O than from S to the cationic center in the 90°-twisted transition state for bond rotation, which may be due to a larger *p*-character for nonbonded electrons of O than of S at the twisted geometry where π-overlap is minimal.

There is a *decrease* in the intrinsic reaction barrier for the addition of solvent to $4\text{-}MeOC_6H_4CH(CH_3)^+$ with replacement of π-electron donation from the 4-methoxybenzyl ring by π-electron donation from the α-methoxy group in $4\text{-}MeOC_6H_4CH(OMe)^+$ (Figure 3).[1,2] This suggests that stabilization by π-electron donation of the reaction transition states, where the cationic center is partly rehybridized, is more effective for electron donation from an α-MeO than from a 4-methoxybenzyl group.

3.7. Description of the Barrier - Part 2

The experiments described in this section provide information about substituent effects on the barrier heights to carbocation-nucleophile combinations and further insight into the nature of the barrier. The most important conclusion from this work is that increasing resonance stabilization of substituted benzyl carbocations causes the rise in energy on approaching the transition state to become increasingly steep (Figure 2), and the barrier height to become increasingly large. This was illustrated in Figure 3 as increasing Marcus intrinsic barriers with increasing stabilization of α-substituted 4-methoxybenzyl carbocations by electron donation from the 4-methoxyphenyl ring. It also provides a possible explanation for imbalances observed in the fractional expression of inductive and resonance substituent effects on the rate constants for carbocation-nucleophile combination (Figure 4). The observation of increasing intrinsic barriers to carbocation-nucleophile combination with increasing π–electron donation to the cationic center supports the proposal made in Section 2.2 that these reactions be viewed as nucleophilic additions to weak π-bonds. There are several effects that are proportional to the strength of the partial π-bond at the electrophilic carbon of the reactant and that may contribute to the observed reaction barrier.

(1) Part of the barrier may represent electronic repulsion between the nucleophile and the partly-filled orbital of the cationic center, which is expected to increase with increasing electron donation to this center.

(2) Part or all of the barrier might be due to a difference in the stabilization of the transition state that results from partial formation of a bond to the nucleophile and the destabilization that results from loss of resonance electron donation to the electrophilic carbon (*i.e.*, loss of resonance stabilization, Section 3.4). The barrier would then correspond to the energy requirement for electronic reorganization on progression from ground to transition state. The observation of substantially different rate constants for addition of water to α-oxygen- and α-sulfur-stabilized carbocations of comparable equilibrium stability suggests that the barriers to these reactions are indeed sensitive to the changes in resonance stabilization of the transition state (Section 3.6).[11]

(3) Part of the barrier to nucleophile addition to resonance-stabilized carbocations might be due to the

requirement to localize an electron pair at the electron-donating substituent. This will have the largest effect on the barrier height for reaction of neutral electrophiles such as **9** and **10**, where localization of the electron pair is accompanied by the buildup of negative charge at the electron-rich substituent which may be stabilized by the presence of a general acid catalyst.[95b]

There have been few comparisons of the relative reactivity of nucleophiles in additions to carbocations and to the carbonyl group, because of difficulties in extracting microscopic rate constants for conversion of the carbonyl group to the tetrahedral nucleophile adduct from macroscopic observed rate constants for multistep carbonyl group addition reactions. The best comparison is from a study of the uncatalyzed addition of nucleophiles to acetyl chloride, where the high nucleofugality of chloride ion insures that formation of the tetrahedral nucleophile adduct is rate determining for the reaction.[84b] There is a reasonably good logarithmic correlation between rate constants for nucleophile addition to acetyl chloride and N_+ values for addition to carbocations, with a slope of 0.47 (correlation coefficient = 0.91).[84b] This shows that the relative order of reactivities of nucleophiles towards addition to carbocations and to acetyl chloride are about the same, but that rate constants for reactions of acetyl chloride are less sensitive to changes in nucleophilicity, for reasons that are not well understood.

The similarity between the tendency of increasing resonance stabilization of charged intermediates to increase the intrinsic barriers to nucleophilic additions to carbocations and to protonation of carbanions[40,49,50,53] is striking, and it points to similar explanations for the two phenomena. In the case of carbanion protonation, there is a good correlation between the intrinsic reaction barrier and π-electron donation to the neighboring electron-sink. The barrier to these reactions might therefore be attributed to the difference in the stabilization of the transition state that results from development of bonding interactions to the proton donor and the energy price paid in localizing negative charge at the reacting carbon.

4. REACTIVITY-SELECTIVITY RELATIONSHIPS

The relative barrier heights for addition of two nucleophiles Nu1 and Nu2 to a carbocation is conveniently expressed as the ratio of rate constants for the two addition reactions, $k_{\mathrm{Nu1}}/k_{\mathrm{Nu2}}$, which is also referred to as the nucleophile selectivity. Nucleophile selectivities for additions to carbocations may be calculated from the yields of the nucleophile adducts R-Nu1 and R-Nu2 obtained from stepwise $D_N + A_N$ (S_N1)[68] nucleophilic

$$k_{\mathrm{Nu1}}/k_{\mathrm{Nu2}} = [\mathrm{R\text{-}Nu1}][\mathrm{Nu2}]/[\mathrm{R\text{-}Nu2}][\mathrm{Nu1}] \qquad (3)$$

substitution at R-X (Eq 3), or as the ratio of absolute rate constants for addition of the nucleophiles to carbocations generated under stable ion conditions[3,4] or by laser flash photolysis.[28,85-91] The discussion in this section will focus on selectivities determined as product rate constant ratios (Eq 3); but there is fair to good agreement between nucleophile selectivities determined by this method and by direct measurement, and few important differences in the interpretations of data obtained by these different methods.

4.1. Simple Relationships Between Carbocation Lifetime and Nucleophile Selectivity

It is generally true that nucleophilic reagents exhibit large selectivities towards relatively stable carbocations and smaller selectivities towards highly unstable carbocations. However, this generalization ignores the complexity of these relationships, where in some cases small changes in electrophile reactivity lead to large changes in nucleophile selectivity,[92,93] and in others large changes in electrophile reactivity lead to small or negligible changes in selectivity.[3-5] Kemp and Casey suggested that sharp changes in selectivity (k_{Nu1}/k_{Nu2}) with changing electrophile reactivity are expected when the larger rate constant is diffusion-limited and independent of changes in electrophile reactivity and the smaller is activation-limited, because then all of the change in the smaller, activation-limited, rate constant will be expressed as a change in the nucleophile selectivity.[94] Jencks then explained how and why reactivity-selectivity relationships should depend upon the absolute reactivity of the carbocation with solvent (k_s, s^{-1}).[95a] Figure 8 illustrates this for partitioning of carbocations between reaction with azide ion (k_{az}, M^{-1} s^{-1}) and with solvent. Jencks and Richard confirmed the existence of the structure-reactivity relationships implied by Figure 8, first for partitioning of ring-substituted 1-phenylethyl carbocations between reaction with azide ion and aqueous trifluoroethanol,[15,96] and later for the

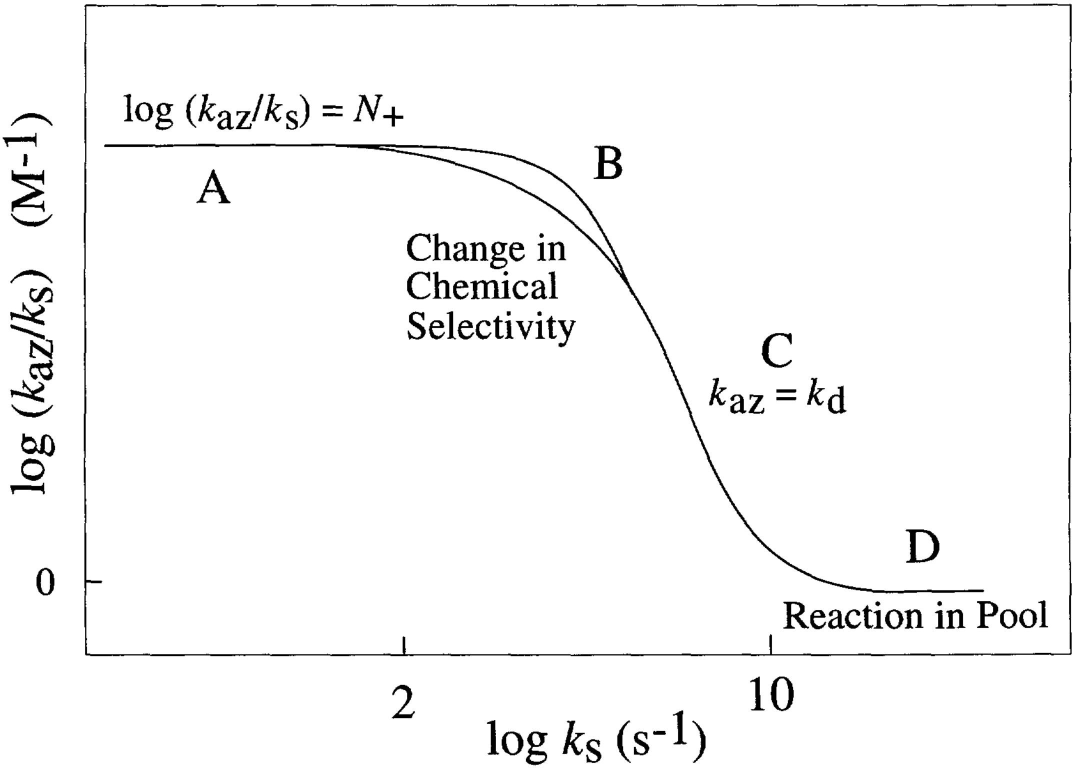


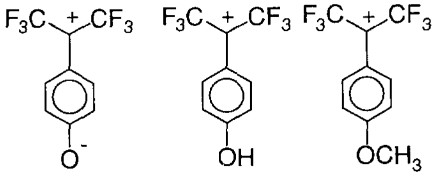
Figure 8. Dependence of the azide ion selectivity (k_{az}/k_s, M^{-1}) on carbocation reactivity (k_s, s^{-1}) towards largely aqueous solvents. The upper solid line is for a hypothetical reaction where the nucleophile selectivity remains constant as k_{az} approaches the diffusion-controlled limit. The difference between the upper and lower solid lines illustrates a decrease in azide ion selectivity due to a Hammond effect.

reactions of several other nucleophilic reagents.[16,97] Finally, Ta-Shma and Rappoport have shown that virtually all of the reactivity-selectivity data for stepwise nucleophilic substitution reactions of azide ion and solvent with alkyl derivatives can be rationalized by one of the following four reactivity-selectivity relationships for the carbocation intermediates (Figure 8).[98,99]

Relationship A. Constant nucleophile selectivities are observed for reaction of azide ion, solvent, and a wide variety of other nucleophilic reagents with highly resonance-stabilized triarylmethyl carbocations, tropylium ions, and related electrophilic reagents.[3,4] These constant selectivities are expressed in abbreviated form as the N_+ value for the nucleophilic reagent, where $N_+ = \log (k_{Nu}/k_s)$, and k_s is the pseudo-first-order rate constant for reaction of solvent. A value of $N_+ \approx 6$ has been determined for azide ion in aqueous solution.[26-28]

Constant nucleophile selectivities are observed for the addition of alkenes to diarylcarbenium ions of increasing reactivity when the rate constant for reaction for the more nucleophilic alkene is $\leq 5 \times 10^7$ M^{-1} s^{-1}.[134]

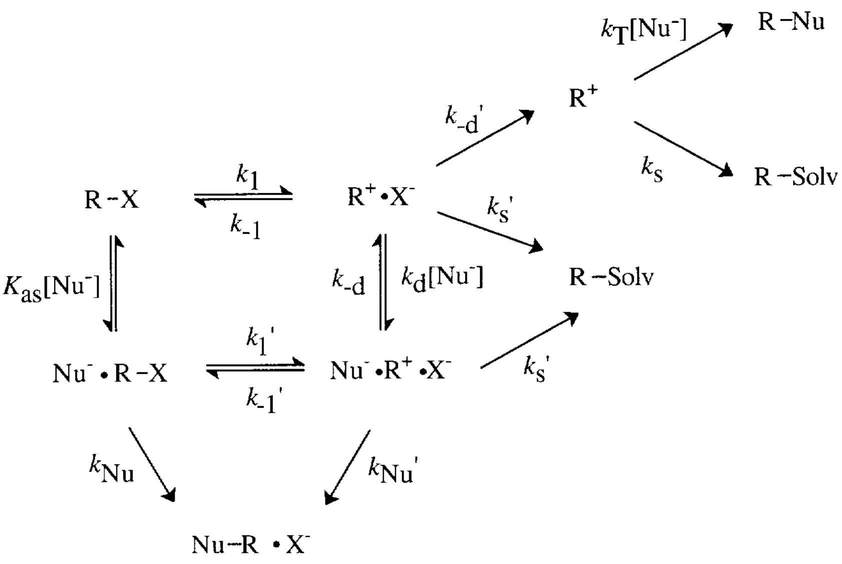
Relationship B. It was once thought that a constant difference in the relative *chemical* barriers to carbocation-nucleophile combination is maintained right up to the point where the reaction of azide ion reaches the diffusion-controlled limit.[3,100] However, the results of an extremely thorough laser flash photolysis study have shown that small, but significant, decreases in the nucleophile selectivity k_{az}/k_s, (M^{-1}) are observed for the reaction of azide ion with ring-substituted triarylmethyl and diarylmethyl carbocations *before* k_{az} reaches the diffusional value of *ca.* 5×10^9 M^{-1} s^{-1}.[28] The decrease in chemical selectivity is illustrated by the difference in the upper and lower solid lines in Figure 8. The simplest explanation for the decreasing chemical selectivity with increasing carbocation reactivity is that it represents a Hammond-type shift to an earlier transition state for the nucleophile addition reaction.[101] Hammond effects have also been reported for the activation-limited reactions of amines with ring-substituted triarylmethyl and diarylmethyl carbocations[89] and with ring-substituted 1-phenyl-2,2,2-trifluoroethyl carbocations;[102] for the reactions of alkyl alcohols and alkyl carboxylate ions with ring-substituted 1-phenylethyl[16] and 1-phenyl-2,2,2-trifluoroethyl carbocations;[102] and for the reaction of halide ions with **4-ROC$_6$H$_4$C(CF$_3$)$_2$$^+$**.[20]



4-ROC$_6$H$_4$C(CF$_3$)$_2$$^+$

Relationship C. The selectivity k_{az}/k_s (M^{-1}) decreases sharply with increases in carbocation reactivity once k_{az} levels off at the diffusion-controlled limit of *ca.* 5×10^9 M^{-1} s^{-1}. The nucleophile selectivity now provides a measure of the chemical barrier to the activation-limited reaction of solvent relative to the small barrier to diffusional formation of an encounter complex between the carbocation and azide ion. Sharp changes in nucleophile selectivity with changing carbocation reactivity are observed, because the entire change in k_s (s^{-1}) is now expressed as a change in the nucleophile selectivity. Such sharply changing azide ion selectivities with increasing cation reactivity have been reported for the reactions of ring-substituted diarylmethyl,[28] 1-phenylethyl,[15,96] 1-phenyl-2,2,2-trifluoroethyl,[42] cumyl,[103] α-alkoxybenzyl,[10,45] and tris(aryloxy)methyl[104] carbocations. These large reactivity-selectivity effects provide, in turn, strong evidence for a diffusion-controlled reaction of azide ion, and they allow for calculation of absolute rate constants k_s (s^{-1}) from the product selectivity k_{az}/k_s (M^{-1}) using $k_{az} = k_d = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-controlled reaction of azide ion. Direct measurement of k_{az} for the reactions of ring-substituted diarylmethyl[28] and α-substituted 4-methoxybenzyl carbocations[90] generated by laser flash photolysis has shown that the uncertainty in the diffusion-controlled rate constants for the reactions of azide ion, and in the rate constants k_s calculated by use of k_{az} as a "clock" for the solvent reaction, is only ±20%.

Relationship D. The product rate constant ratio k_{az}/k_s (M^{-1}) for stepwise solvolysis of R-X decreases with increasing carbocation reactivity until the carbocation becomes so reactive that the ion pair precursor to the free cation is captured by solvent before there is significant escape to form free ions ($k_s' > k_{-d}'$, Scheme 9). At this point, a small limiting selectivity is observed that reflects the relative yields of the solvent adduct from direct addition of solvent to an ion pair intermediate (k_s') and of nucleophile adduct from collapse of a triple ion complex (k_{Nu}'). In aqueous solution, since $k_s' > k_{-d}'$ for diffusional separation of the leaving group, then $k_s' > k_d$[Nu] for diffusional encounter of the ion pair with added nucleophilic reagent, because association constants for formation of complexes between ions in water are small ($K_{as} = k_d/k_{-d} \approx 0.1$ M^{-1}).[105] Therefore, the nucleophile adduct forms by a preassociation mechanism involving reaction of the nucleophile already present in an encounter complex with substrate at the time of ionization (K_{as}, k_1', k_{Nu}', Scheme 9).[16]



Scheme 9

The selectivity for the (apparently) stepwise reactions of ring-substituted cumyl derivatives with azide ion in aqueous trifluoroethanol decreases to $k_{az}/k_s = 0.7$ M^{-1} for reaction of 3-fluorocumyl chloride, and remains constant as the ring substituents are made more electron-withdrawing, up to 3,5-di-CF_3.[103] The significance of this relatively large limiting selectivity is unclear. The limiting selectivity is consistent with $K_{as} = 0.7$ M^{-1} for formation of an encounter complex between azide ion and substrate (Scheme 9), but this is an unusually large value for association between solutes in a largely aqueous solution.[105] The product selectivity ratio k_{az}/k_s (M^{-1}) could include a contribution from bimolecular nucleophilic substitution by azide ion (k_{Nu}), or assistance by azide ion to ionization of the substrate ($k'_1 > k_1$, Scheme 9). However, azide ion has no effect on the observed pseudo-first-order rate constants for the reactions of cumyl derivatives in aqueous trifluoroethanol at constant high ionic strength maintained with perchlorate ion, so that if there were a bimolecular reaction of azide ion, its effect on the overall reaction rate is masked by a negative specific salt effect. Finally, data for the stepwise nucleophilic substitution reaction of azide ion with 1-(4-methoxyphenyl)-2,2,2-trifluoroethyl iodide are also consistent with $K_{as} = 0.7\ M^{-1}$ for formation of an encounter complex between azide ion and the neutral substrate, suggesting that there may indeed be an unexpectedly large stability of these encounter complexes.[106]

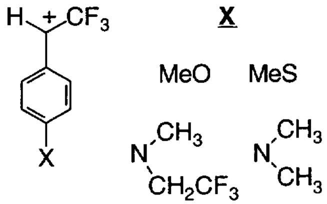
A significant fraction of the carbocation intermediate of the reaction of 1-(4-methylphenyl)ethyl derivatives reacts with solvent before diffusional separation of leaving group ($k_s' > k_{-d}'$, Scheme 9).[15,16] Acetate ion is 10-fold less reactive than azide ion towards this intermediate, which is consistent with a limiting selectivity of $k_{Ac}/k_s < 0.1\ M^{-1}$ for the nucleophile reaction, and $K_{as} < 0.1\ M^{-1}$ for formation of an encounter complex between acetate ion and substrate (Scheme 9).[16] The different limiting selectivities observed for the reactions of acetate and azide ions require there to be different thermodynamic barriers to formation of their reactive encounter complexes with aliphatic substrates. A simple explanation for this difference is that it reflects the stronger solvation of acetate than of azide ion, and a correspondingly larger barrier to removal of a single molecule of solvent from solvated acetate ion to free an electron pair to enable it to participate in a chemical reaction (see Section 5).

4.2. The Appearance of Hammond Effects

The most intriguing feature of Figure 8 is the transition from azide ion selectivities that are independent of carbocation reactivity (region A), to selectivities that decrease with increasing reactivity of the carbocation due to a Hammond effect (region B). There are a number of other examples of Hammond effects on carbocation-nucleophile combination that appear as the barrier to the reaction is progressively lowered.

(1) Alkylamines show constant nucleophile selectivities towards the least reactive triarylmethyl carbocations,[4] but substantially smaller selectivities for *activation-limited* addition to the more highly reactive triarylmethyl carbocations[89] and to the 1-(4-dimethylaminophenyl)-2,2,2-trifluoroethyl carbocation.[102]

(2) Pronounced curvature is observed in plots of β_{nuc} for *activation-limited* reactions of alkyl alcohols and alkyl carboxylates with 4-substituted 1-phenyl-2,2,2-trifluoroethyl carbocations (**27**) against log k_s for reaction of the carbocations with a solvent of 50/50 trifluoroethanol/water.[102] Reactions with small kinetic barriers and large rate constants show sharp changes in selectivity with changing carbocation reactivity. However, the initial change in β_{nuc} is so sharp that a linear dependence on log k_s cannot be maintained over an extensive range of carbocation reactivity, because this would require that values of β_{nuc} rapidly approach 1.0. Instead β_{nuc} appears to approach (but not attain) a limiting value that is well below 1.0.



27

It has been suggested that general base catalysis by solvent might somehow contribute to changes in selectivity for reactions of neutral nucleophiles.[107] However, general base catalysis by solvent of its own reaction is only barely permitted by Jencks' *libido* rule,[108] and has been shown to be negligible in several relevant cases (Section 4.3).

These data may be rationalized by consideration of the following structure-reactivity effects:

(1) A first-derivative effect for nucleophile selectivity which may be measured as β_{nuc} for reaction of a structurally homologous series of nucleophiles. The first-derivative effect is equal to the first derivative (Eq 4) of the Marcus equation (Eq 1).[39]

$$\beta_{nuc} = \partial \log k_{Nu}/\partial \Delta G^{o} = 0.5 + \Delta G^{o}/8\Lambda \tag{4}$$

The significance of β_{nuc} is relatively straightforward, provided β_{nuc} is determined for polar substituent effects on the reactivity of a set of structurally homologous nucleophiles, such as alkyl alcohols. Here, β_{nuc} provides a measure of the fraction of the polar substituent effect on ΔG^{o} for ionization of alkyl alcohols which is expressed on $\Delta G^{\ddagger}$ for addition of the same alcohols to carbocations. The ionization of alkyl alcohols is used as a reference reaction, where polar substituents experience a full unit change in charge at the nucleophilic oxygen. Operationally, β_{nuc} measures the fractional expression of the equilibrium polar substituent effect and will vary from zero for a reactant-like transition state, to 1.0 or greater for a product-like transition state. The observed values of β_{nuc} provide a measure of the change in the polar interaction of the substituent with the reaction center on moving to the transition state, which in turn depends upon the "effective positive charge" at oxygen in the transition state.[109] The "effective charge" at oxygen will increase with increasing bond formation to the alcohol nucleophile in the transition state; however, the precise relationship between the experimental term β_{nuc} and properties of the transition state such as charge development at, or bond formation to, the oxygen nucleophile is not well understood.[34]

(2) A second-derivative effect, $\partial\beta_{nuc}/\partial\Delta G^{o}$, that describes the change in β_{nuc} with changing thermodynamic driving force for the carbocation-nucleophile combination (Eq 5). The second-derivative term describes the change in transition state structure with changing thermodynamic driving force.[35-37] The change from small values of β_{nuc} for addition of alcohols to unstable carbocations, to progressively larger values of β_{nuc} for addition to carbocations of increasing stability, reflects the shift from a reactant-like transition state to transition states with increasing "effective positive charge" at the alkoxy-oxygen and fractional development of the covalent carbon-oxygen bond of the product. This change corresponds to a simple Hammond-type shift to a more product-like reaction transition state illustrated by Figure 9A.

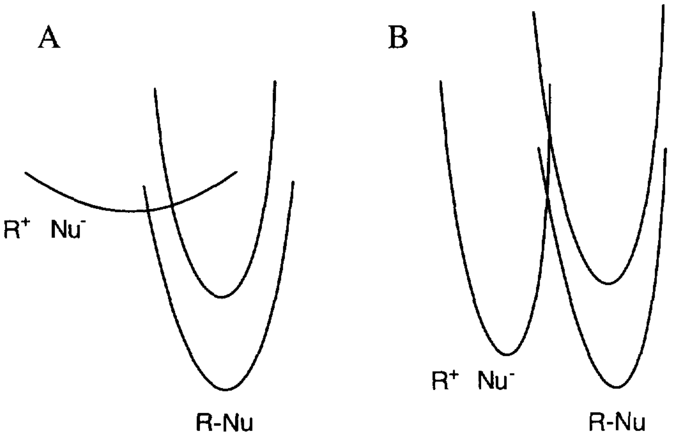


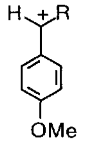
Figure 9. Hypothetical reaction energy profiles for: (A) A reaction with a relatively small intrinsic barrier and a transition state that shows sharp movement with changing ΔG^{o}. (B) A reaction with a relatively large intrinsic barrier that shows much smaller movement with changing ΔG^{o}.

$$\partial\beta_{nuc}/\partial\Delta G^{o} = 1/8\Lambda \tag{5}$$

(3) There must also be a third-derivative effect[110] on the second-derivative term, because the change in the second-derivative term is large for the reaction of unstable carbocations (sharp changes in nucleophile selectivity with changing reactivity), and approaches zero for reaction of highly stabilized carbocations (constant selectivities equal to the N_+ value for the nucleophile).[102] The change from an experimentally significant second-derivative term for the reaction of relatively weakly resonance-stabilized carbocations, to $\partial\beta_{nuc}/\partial\Delta G^{o} \approx 0$ for strongly resonance-stabilized carbocations is consistent with a sharp increase in the intrinsic barrier Λ for these reactions.

These results may be rationalized qualitatively by the changes in the reaction coordinate profile diagrams shown in Figure 9, where changes in nucleophile selectivity with changing thermodynamic driving force are represented as Hammond-type shifts of the reaction transition states. Figure 9A shows coordinates with shallow curvature (Section 3.1) for carbocation-nucleophile combinations with a relatively small intrinsic barrier Λ and a very mobile transition state; and Figure 9B shows coordinates with steep curvature for addition of nucleophiles to strongly resonance-stabilized carbocations where the intrinsic barrier Λ is relatively large and the position of the transition state is more or less fixed (see Eq 5).

There is a striking contrast between the sharply changing nucleophile selectivities (β_{nuc}) for reactions of substituted alkyl alcohols as the stability of 1-phenylethyl[16] and 1-phenyl-2,2,2-trifluoroethyl carbocations[102] is varied by changes in the ring substituent, and the constant nucleophile selectivities observed as the stability of 4-methoxybenzyl carbocations **28** is varied by changing the α-substituent.[5] The constant selectivities cannot be explained by a consideration of differential steric or electrostatic effects on the reaction barrier, because these differences are small for reaction of the α-CH_2F and α-CO_2Et substituted carbocations. These results are consistent with the proposal that substituent effects on nucleophile selectivity depend both on the effect on the thermodynamic driving force (ΔG^{o}) and on the Marcus intrinsic barrier (Λ, Eqs 4 and 5). According to this proposal, the addition of electron-withdrawing α-substituents to **28** causes ΔG^{o} for the addition of nucleophiles to increase, which decreases nucleophile selectivity, and Λ to increase (Figure 3) which leads to an opposing increase in selectivity, with the net result being cancellation of the opposing effects and constant nucleophile selectivities (β_{nuc}).



28

R

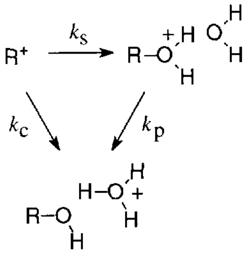
CH_3 CH_2F CHF_2

CF_3 CO_2Et

Constant nucleophile selectivities are observed for addition of alkenes to diarylcarbenium ions of increasing reactivity when the rate constant for reaction of the more nucleophilic alkene is ≤ 5 x 10^7 M^{-1} s^{-1}, but the selectivity decreases as this rate constant is increased above 5 x 10^7 M^{-1} s^{-1}.[134] The limiting rate constant for diffusion-controlled reactions of alkenes in organic solvents has not been cleanly defined, so that it is uncertain whether the observed decrease in selectivity is due an underestimate of the chemical reactivity of the more nucleophilic alkene (whose reaction is partly diffusion-controlled), or to a change in the chemical selectivity for activation-limited reactions of alkenes. If the observed rate constants of 5 x 10^7 M^{-1} s^{-1} for these reactions are partly diffusion-limited, then the rate constant for a diffusion-controlled reaction must be considerably smaller than the values of (5-7) x 10^9 M^{-1} s^{-1} observed for the reaction of azide ion with diaryl- and triarylmethyl carbenium ions.[28]

4.3. General Base Catalysis

Nucleophile selectivities may be affected by general base catalysis of one or both of the nucleophile addition reactions. It has been suggested that changes in nucleophile/solvent selectivities might be due to variations in third-order rate constants for general base catalysis by solvent of the addition of solvent (Scheme 10).[107] However, there is at best only a small advantage to coupling of the nucleophile addition (k_s) and proton transfer (k_p) steps in a concerted reaction (k_c), because there is not a large difference in the stabilities of the oxonium ion intermediate and the hydronium ion-alcohol complex (Scheme 10).[111] This suggests that there can not be a large advantage to a concerted mechanism, which avoids formation of the oxonium ion, and provides a rational for the following experimental results which show that solvent additions often follow a stepwise pathway.



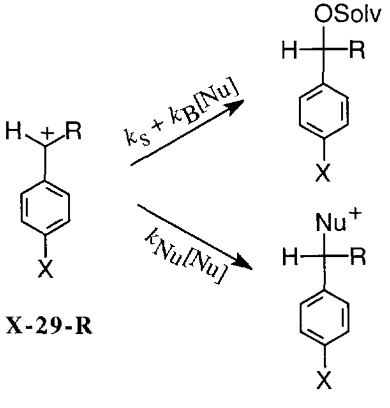
Scheme 10

(1) Concerted general base catalysis by substituted quinuclidines of the addition of water to ring-substituted triarylmethyl carbocations has been observed.[111] However, the calculated rate constant for a (hypothetical) third-order water-catalyzed addition of water to the *bis*-(4-dimethylamino)triphenylmethyl carbocation shows an 800-fold positive deviation from the Brønsted plot of rate constants for the amine catalysts.[111] The large positive deviation for the solvent-catalyzed reaction of solvent is consistent with a change from concerted termolecular amine-catalyzed addition of water to uncatalyzed bimolecular reaction of water on moving from strongly basic amines catalysts to water alone.

(2) The inverse solvent deuterium isotope effect on the specific-acid-catalyzed heterolysis of diferrocenylphenylmethanol $[(k_H)_{HOH}/(k_H)_{DOD} = 0.54]$[112] is consistent with preequilibrium protonation of the alcohol followed by bond cleavage to form water and a ferrocenyl-stabilized carbocation. This is the microscopic reverse of uncatalyzed addition of water to the carbocation to form an oxonium ion, which undergoes deprotonation by solvent. The small solvent deuterium isotope effects on addition of water to ferrocenyl-stabilized[113] carbocations and to the trianisylmethyl ($k_{HOH}/k_{DOD} \approx 1.2$) are likewise consistent with direct, uncatalyzed, addition of water to the carbocation.[113,114]

(3) An extensive body of evidence supports a stepwise mechanism for specific-acid-catalyzed cleavage of acetals and ketals.[115]

General base catalysis by added nucleophilic reagents will be detected only when the rate constants for the Brønsted base (k_B) and Lewis base (k_{Nu}) reactions are similar, or when the nucleophile adduct is unstable (Scheme 11). The observed nucleophile selectivity k_{az}/k_{TFE} for partitioning of **MeO-29-CH$_3$** between reaction with azide ion and trifluoroethanol in 50/50 trifluoroethanol/water decreases about two-fold as the concentration of acetate ion is increased from zero to 0.50 M, due to catalysis by acetate ion of the reaction of trifluoroethanol.[116] Catalysis can be detected because the total yield of nucleophile adduct at the largest acetate ion concentration is only 60%.



X-29-R

Scheme 11

It is not possible to detect general base catalysis by amines of the addition of water to **Me_2N-29-CF_3**, because the nucleophilic addition reaction is very fast ($k_{Nu} >> k_B$).[102] Catalysis by substituted quinuclidines of the addition of water to triarylmethyl carbocations can be detected because the nucleophile adducts (quaternary ammonium ions) are unstable.[111]

The hypothetical rate constants for the solvent-catalyzed addition of solvent (aqueous trifluoroethanol) show small *negative* deviations from Brønsted correlations of third-order rate constants for alkyl carboxylate ion-catalyzed addition of solvent to **MeO-29-CH_3**[116] and **Me_2N-29-CH_3**.[110] By contrast, large positive deviations are observed for the hypothetical rate constant for water from Brønsted correlations of rate data for the tertiary amine-catalyzed reactions of triarylmethyl carbocations.[111] These results show that it is relatively easier to detect catalysis by alkyl carboxylate ions than by tertiary amines against the background of the uncatalyzed solvent addition reaction: this reaction is relatively slow compared to catalysis by the carboxylate anions, and fast compared to catalysis by the neutral amines. The greater effectiveness of carboxylate ions than of amines as general base catalysts is consistent with stabilization of the reaction transition state by electrostatic interactions between the carbocation and the anionic catalyst. Similarly, electrostatic interactions between a developing carboxylate anion and oxocarbenium ion provides appreciable stabilization of the transition state for carboxylic acid-catalyzed hydrolysis of vinyl ethers.[117]

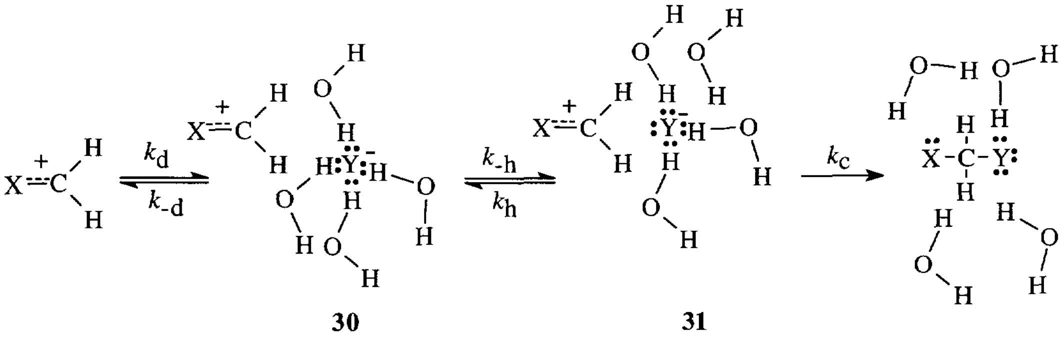
Sharp changes are observed in the Brønsted reaction coefficient β for general base catalysis by alkyl carboxylates of alcohol addition to **X-29-CH_3** with changing pK_a of the alcohol nucleophile and changing stability of **X-29-CH_3**; in β_{nuc} for addition of alkyl alcohols with changing pK_a of the alkyl carboxylate catalyst and changing carbocation stability; and in the Hammett reaction constant ρ for changing reactivity of the base catalyst and of the alcohol.[110] These data have been rationalized by use of two-dimensional reaction coordinate diagrams for termolecular general-base-catalyzed addition of alkyl alcohols to **X-29-CH_3**.[110,35] The data require the existence of both second- and third-derivative structure-reactivity effects, similar to those discussed in the previous section for simple carbocation-nucleophile combinations. The second-derivative structure-reactivity coefficients for changing β, β_{nuc}, and ρ with changing reactivity of nucleophile, base catalyst, and electrophile are relatively small when the reaction barrier is relatively large, but they increase on progression to reactions with very low barriers. The changing second-derivative terms are third-derivative effects (*e.g.*, Eq 5), which are relatively difficult to detect because they only appear as the barrier to a reaction is made very small, and the curvature of the energy surface becomes very shallow (Figure 9).

In conclusion, there is a large body of experimental data that describe how nucleophile selectivity changes as the reactivity of a carbocation towards nucleophilic addition of the solvent water varies by *ca.* 10^{15}-fold. In this review, the changes in selectivity observed for activation-limited additions of nucleophiles have been rationalized using a crude model which considers the effects of changing both the thermodynamic driving force (ΔG^o) and the intrinsic barrier (Λ) on the position of the transition state along a simple one-dimensional reaction coordinate profile. Further development of this and other models would improve our understanding of β_{nuc} and how it changes, and they might serve to place the Marcus relationships between β_{nuc}, ΔG^o and Λ (Eqs 4 and 5) on a firmer theoretical footing.

5. SOLVENT EFFECTS ON CARBOCATION REACTIVITY

Solvation must have profound effects on the reactivity of carbocations, but at present these are only poorly understood. However several important conclusions may be drawn from recent studies of carbocation-nucleophile combination reactions.

(1) There is only a small barrier to moving from fully solvated nucleophilic anions to species competent to form covalent bonds with reactive electrophiles. For example, the rate constants for the reaction of azide ion with ring-substituted diarylmethyl carbocations in largely aqueous solution increase with increasing carbocation reactivity up to the diffusion-controlled limit.[28] This outcome shows that the barrier to the solvent reorganization that positions the ions in a contact ion pair so that they may react to form a covalent bond(k_{-h}, Scheme 12) is even smaller than the barrier to diffusional separation of the solvent-separated ion pair to form free ions (k_{-d}). [The observed values of $K_{as} = k_d/k_{-d}$ are less than 1.0 (see below) so that $k_{-d} > k_d$]. In other words, the solvent reorganization on moving from the solvent-separated ion pair **30** to the intimate ion pair **31** in water is relatively small, and involves cleavage of perhaps only a single hydrogen bond so that nearly full solvation of the nucleophile is maintained in the intimate ion pair.



Scheme 12

(2) The reactivity of alkylamines towards the 1-(4-methylthiophenyl)ethyl carbocation *decreases* about three-fold on moving from weakly basic trifluoroethylamine to strongly basic ethylamine; and the absolute rate constants for these reactions are 30-90-fold smaller than that for the diffusion-limited reaction of azide ion.[118] These data are consistent with the conclusion that the barrier to these reactions is composed primarily of that for cleavage of a solvent-amine hydrogen bond, which is required to move from a solvent-separated to an intimate ion-dipole pair (k_{-h}), so that the increase in the barrier with increasing amine basicity is due to the increased difficulty of cleavage of a solvent-amine hydrogen bond. Similar results have been reported for the reactions of amines with ring-substituted diarylmethyl and triarylmethyl carbocations.[89] One conclusion from the latter work was that desolvation of the amine (k_{-h}, Scheme 12, but for an ion-dipole pair) occurs prior to formation of an encounter complex with substrate, and that the "desolvated amine" forms a contact ion-dipole pair with the electrophile by a pathway that avoids formation of a solvent-separated ion-dipole pair. This proposal deserves further consideration. However, no evidence compels abandonment of solvent-separated ion or ion-dipole pairs as discrete intermediates in carbocation-nucleophile combination, and a large body of experimental data is

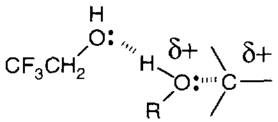
consistent with the formation of these species as intermediates on the pathway for diffusional separation of ion pair intermediates of solvolysis reactions.[119,120]

(3) The rate constant for addition of water to an *ortho*-sulfonyl methyl ester-substituted trityl carbocation is only 3-fold larger than that for addition to the corresponding intramolecular ion pair between the trityl carbocation and its *ortho*-sulfonate substituent.[27] There is indirect kinetic evidence that the 1-(4-methoxyphenyl)-2,2,2-trifluoroethyl carbocation-bromide ion pair is only 3-6 fold less reactive towards nucleophilic addition of water than the free carbocation.[106] These results show that the attenuation of carbocation reactivity by surrounding solvent water is so large that replacement of a water molecule with an anion has relatively little further effect on carbocation reactivity.

(4) The effect of a change from water to nonaqueous solvents such as dimethylsulfoxide or acetonitrile on the activation barriers for the addition of nucleophiles to stable triarylmethyl carbocations such as malachite green and crystal violet ($\Delta\Delta G^{\ddagger}$) has been estimated to be equal to the effect of hydrogen bonding on the stability of the nucleophile in the aqueous compared with the nonaqueous solvent ($\Delta\Delta G_{HB}$).[121,122] These data are consistent with a nearly complete loss of hydrogen bonding to water on progression from the reactants to the transition state; that is, the transition state is late with respect to changes in solvation at the nucleophile. Rate constants for the addition of nucleophiles to more reactive carbocations such as the trityl cation and the retinyl cation[122] show smaller sensitivities to changes in solvent; and this trend is consistent with a Hammond-type shift to an earlier transition state in which part of the solvation of the nucleophile is maintained.

(5) The effects of changing solvent on carbocation reactivity are complex because these changes affect both the electrophilic reactivity of the carbocation and the overall nucleophilic reactivity of the bulk solvent. There is only a small effect of changing solvent polarity on its reactivity in nucleophilic addition to the 1-(4-methoxyphenyl)ethyl carbocation. For example, there is only a 3-fold increase in the reactivity of methanol towards this cation for a change from 10% to 80% methanol in water. This change in solvent causes a larger (5-8)-fold increase in the second-order rate constant for the reaction of water, as well as a decrease in the selectivity for partitioning between reaction with methanol and water.[15] There is a much larger reduction in the reactivity of methanol, water, and trifluoroethanol and increases in the constant ratios k_{MeOH}/k_{TFE} and k_{HOH}/k_{TFE} on changing from 20/80 (v/v) to 90/10 (v/v) trifluoroethanol/water. These results have been attributed to the tendency of trifluoroethanol, a strong hydrogen bond donor and weak acceptor, to reduce the nucleophilic reactivity of hydroxylic solvents by strengthening the hydrogen bond to the lone pair of electrons at the nucleophile (**32**), and by weakening the solvation of the developing positive charge in the transition state through hydrogen bonding (**33**).[15] Trifluoroethanol is itself a nucleophile and should be particularly sensitive to the second of these effects because its high acidity favors such solvation and base catalysis in its nucleophilic reactions.[110,116] The larger decrease in k_{TFE} than in k_{HOH} and k_{MeOH} is consistent with a dominant role for this effect in reducing the bulk nucleophilicity of solvent.

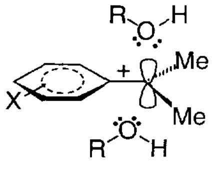
32



33

(6) Experimental and theoretical studies show that carbocations are strongly stabilized by solvation by water[123-125] and by other solvents.[126] The 50 kcal/mol stabilizing effect of water appears to be due to nonspecific charge-dipole interactions.[25] It has also been proposed that carbocations are specifically stabilized by

a Lewis acid-base interaction between a nonbonding electron pair from solvent and the unoccupied *p*-orbital at carbon (**34**). This interaction is referred to as nucleophilic solvation and has been proposed to stabilize the transition state for formation of carbocations in solvolysis reactions.[127-129]



34

Experiments have not provided definitive evidence for the existence of nucleophilic solvation, but instead show that this interaction is much weaker than the corresponding Brønsted acid-base interactions between hydrogen bond donors and acceptors. A near unit slope was observed for a plot of the changes in Gibbs free energy for formation of carbocations from the corresponding alcohols in water against those for a similar reaction in the gas phase, for data that include the strongly resonance-stabilized tropylium and α-methylbenzhydryl carbocations. Therefore, there is little or no attenuation by solvent of the gas-phase substituent effects on the stability of relatively highly resonance-stabilized carbocations.[25,130] A significantly smaller slope (0.7) was observed for a plot of the changes in Gibbs free energy for proton transfer from ring-substituted cumyl carbocations (**34**) to α-methylstyrene in solution against those for the same reaction in the gas phase,[131] so that there is modest solvent attenuation of gas-phase substituent effects on the more unstable ring-substituted cumyl carbocations. However, the corresponding plot of the Gibbs free energies for deprotonation of substituted pyridinium ions in solution against those in the gas phase has a slope of 0.4,[132,133] which shows that solvation of ammonium ions by hydrogen bonding attenuates ring substituent effects more strongly than does solvation of carbocations. The simplest explanation for the larger attenuation of substituent effects on proton transfer between nitrogen acids and bases than on proton transfer between carbon acids and bases is that it reflects the greater covalent character (and resulting transfer of charge onto solvent) for hydrogen bonds between solvent and pyridinium ions than for nucleophilic solvation of carbocations. The observed modest solvent attenuation of substituent effects on the stability of cumyl carbocations certainly includes attenuation of charge-dipole interactions in a solvent of high dielectric constant, but it is impossible to rule out a small contribution from nucleophilic solvation of the carbocation (**34**).

Acknowledgements: The work from the author's laboratory described in this report was supported by Grants GM 39754 and 47307 from the National Institutes of Health. This report was written during a stay at the University of Birmingham that was supported by a grant from NATO. I am grateful to Claude Bernasconi for helpful comments and criticism of this manuscript.

REFERENCES

1. Amyes, T. L.; Richard, J. P. *J. Chem. Soc., Chem. Commun.* **1991**, 200-202.
2. Amyes, T. L.; Stevens, I. W.; Richard, J. P. *J. Org. Chem.* **1993**, *58*, 6057-6066.
3. Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348-354.
4. Ritchie, C. D. *Can. J. Chem.* **1986**, *64*, 2239-2250.
5. Richard, J. P. *J. Org. Chem.* **1994**, *59*, 25-29.
6. Maskill, H.; Jencks, W. P. *J. Chem. Soc., Chem. Commun.* **1984**, 944-946.
7. Maskill, H. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1241-1246.
8. Maskill, H.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 2062-2070.

9. Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 9507-9512.
10. Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888-7900.
11. Jagannadham, V.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 8465-8466.
12. Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1867-1869.
13. Lee, I.; Chung, D. S.; Jung, H. J. *Tetrahedron* **1994**, *50*, 7981-7986.
14. Apeloig, Y.; Karni, M. *J. Chem. Soc., Perkin Trans. 2* **1988**, 625-636.
15. Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361-1372.
16. Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373-1383.
17. Richard, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 6735-6744.
18. Allen, A. D.; Kanagasabapathy, V. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1986**, *108*, 3470-3474.
19. Richard, J. P.; Amyes, T. L.; Bei, L.; Stubblefield, V. *J. Am. Chem. Soc.* **1990**, *112*, 9513-9419.
20. Richard, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 4588-4595.
21. Richard, J. P. *Tetrahedron Lett.* **1989**, *30*, 23-26.
22. Jagannadham, V.; Amyes, T. L.; Richard, J. P. *J. Chem. Soc., Perkin Trans. 2* **1993**, 171-174.
23. Pross, A.; Shaik, S. S. *Acc. Chem. Res.* **1983**, *16*, 363-370.
24. Pross, A. *Adv. Phys. Org. Chem.* **1985**, *21*, 99-198.
25. Wolf, J. F.; Harch, P. G.; Taft, R. W. *J. Am. Chem. Soc.* **1975**, *97*, 2904-2906.
26. Bunton, C. A.; Huang, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 3536-3544.
27. Ritchie, C. D.; Hofelich, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 7039-7044.
28. McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1991**, *113*, 1009-1014.
29. Hoz, S. *J. Am. Chem. Soc.* **1982**, *47*, 3545-3547.
30. Hoz, S.; Speizman, D. *J. Org. Chem.* **1983**, *48*, 2904-2910.
31. Pross, A. *Acc. Chem. Res.* **1985**, *18*, 212-219.
32. Sharma, D. K. S.; Kebarle, P. *J. Am. Chem. Soc.* **1978**, *100*, 5826-5830.
33. Richard, J. P.; Amyes, T. L.; Lee, Y.-G.; Jagannadham, V. *J. Am. Chem. Soc.* **1994**, in press.
34. Williams, I. H. *Chem. Soc. Rev.* **1993**, *22*, 277-283.
35. Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948-7960.
36. Jencks, W. P. *Chem. Rev.* **1985**, 511-527.
37. Jencks, W. P. *Bull. Soc. Chim. Fr.* **1988**, 218-224.
38. Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891-899.
39. Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 475-503.
40. Bernasconi, C. F. *Tetrahedron* **1985**, *41*, 3219-3234.
41. Richard, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 6819-6820.
42. Richard, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 1455-1465.
43. Richard, J. P.; Amyes, T. L.; Stevens, I. W. *Tetrahedron Lett.* **1991**, *34*, 4255-4258.
44. Allen, A. D.; Ambidge, C.; Che, C.; Michael, H.; Muir, R. J.; Tidwell, T. T. *J. Am. Chem. Soc.* **1983**, 2343-2350.
45. Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238-8248.
46. Cozens, F. L.; Mathivanan, N.; McClelland, R. A.; Steenken, S. *J. Chem. Soc., Perkin Trans. 2* **1992**,

2083-2090.

47. Kandanarachchi, P.; Sinnott, M. *J. Am. Chem. Soc.* **1994**, *116*, 5601-5606.
48. Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 3288-3294.
49. Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*, 9-16.
50. Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1991**, *27*, 119-238.
51. Bordwell, F. G.; Boyle, W. J. *J. Am. Chem. Soc.* **1972**, *94*, 3907-3911.
52. Kresge, A. J. *Can. J. Chem.* **1974**, *52*, 1987-1903.
53. Bernasconi, C. F.; Wenzel, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 5405-5413.
54. Tsuno, Y.; Kusuyama, Y.; Sawada, M.; Fujii, T.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3337-3346.
55. Stirling, C. J. M. *Tetrahedron* **1985**, *41*, 1613-1666.
56. Noyce, D. S.; Virgilio, J. A. *J. Org. Chem.* **1972**, *37*, 2643-2647.
57. Liu, K.-T.; Kuo, M.-Y. *Tetrahedron* **1985**, *26*, 355-358.
58. Jones, J.; Kresge, A. J. *Can. J. Chem.* **1992**, *71*, 38-41.
59. Richard, J. P.; Amyes, T. L.; Mizerski, T., unpublished results.
60. Hine, J. *Structural Effects on Equilibria in Organic Reactions*; Wiley-Interscience: New York, 1975; pp 8-10.
61. Schleyer, P. v. R.; Jemmis, E. D.; Spitznagel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 6393-6394.
62. Reed, A. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, 7362-7373.
63. Harcourt, M. P.; More O'Ferrall, R. A. *J. Chem. Soc., Chem. Commun.* **1987**, 823-824. Harcourt, M. P.; More O'Ferrall, R. A. *Bull. Soc. Chim. Fr.* **1988**, 407-414.
64. More O'Ferrall, R. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1098-1099.
65. Wu, Y.-D.; Kirmse, W.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4557-4559.
66. Richard, J. P.; Amyes, T. L.; Rice, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 2523-2524.
67. Bentley, T. W.; Christi, M.; Kemmer, R.; Llewellyn, G.; Oakley, J. *J. Chem. Soc., Perkin Trans. 2,* submitted for publication.
68. Guthrie, R. D.; Jencks, W. P. *Acc. Chem. Res.* **1989**, *22*, 343-349.
69. Apeloig, Y.; Biton, R.; Abu-Freih, A. *J. Am. Chem. Soc.* **1993**, *115*, 2522-2523.
70. Gassman, P. G.; Talley, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 1214-1216.
71. Gassman, P. G.; Saito, K. *Tetrahedron Lett.* **1981**, *22*, 1311-1314.
72. Gassman, P. G.; Saito, K.; Talley, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 7613-7615.
73. Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M. *J. Am. Chem. Soc.* **1980**, *102*, 6640-6641.
74. Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M. *J. Am. Chem. Soc.* **1982**, *104*, 1628-1631.
75. Dixon, D. A.; Charlier, P. A.; Gassman, P. G. *J. Am. Chem. Soc.* **1980**, *102*, 3957-3959.
76. Kirmse, W.; Goer, B. *J. Am. Chem. Soc.* **1990**, *112*, 4556-4557.
77. Boyd, D. R.; McMordie, R. A. S.; More O'Ferrall, R. A.; Kelly, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 7822-7823.
78. (a) Rao, S. N.; More O'Ferrall, R. A.; Kelly, S. C.; Boyd, D. R.; Agarwal, R. *J. Am. Chem. Soc.* **1993**, *115*, 5458-5465. (b) Chiang, Y.; Eliason, R.; Guo, G. H.; Kresge, A. J. *Can. J. Chem.* **1994**, *72*, 1632-1636.

79. Pau, J. K.; Ruggera; M. B.; Kim, J. K.; Caserio, M. C. *J. Am. Chem. Soc.* **1978**, *100*, 4242-4248.
80. Jensen, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 1476-1488.
81. Santry, L. J.; McClelland, R. A. *J. Am. Chem. Soc.* **1983**, *105*, 3167-3172.
82. McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7031-7036.
83. Okuyama, T. *Acc. Chem. Res.* **1986**, *19*, 370-376.
84. (a) Kutzelnigg, W. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 272-295. (b) Palling, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 4869-4876
85. McClelland, R. A.; Kanagasabapathy, V. M.; Steenken, S. *J. Am. Chem. Soc.* **1988**, *110*, 6913-6914.
86. McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1989**, *111*, 3966-3972.
87. McClelland, R. A.; Banait, N.; Steenken, S. *J. Am. Chem. Soc.* **1989**, *111*, 2929-2935.
88. McClelland, R. A.; Cozens, F.; Steenken, S. *Tetrahedron Lett.* **1990**, *31*, 2821-2824.
89. McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1992**, *114*, 1816-1823.
90. McClelland, R. A.; Cozens, F. L.; Steenken, S.; Amyes, T. L.; Richard, J. P. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1717-1722.
91. Steenken, S.; McClelland, R. A. *J. Am. Chem. Soc.* **1989**, *111*, 4967-4973.
92. Raber, D. J.; Harris, J. M.; Hall, R. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1971**, *93*, 4821-4828.
93. Sneen, R. A.; Carter, J. V.; Kay, P. S. *J. Am. Chem. Soc.* **1966**, *88*, 2594-2595.
94. Kemp, D. S.; Casey, M. L. *J. Am. Chem. Soc.* **1973**, *95*, 6670-6680.
95. (a) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161-169. (b) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425-432.
96. Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4689-4691.
97. Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1383-1396.
98. Ta-Shma, R.; Rappoport, Z. *Tetrahedron* **1982**, *23*, 781-784.
99. Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1983**, *105*, 6082-6095.
100. Ritchie, C. D.; Virtanen; P. O. I. *J. Am. Chem. Soc.* **1971**, *94*, 4966-4971
101. Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334-338.
102. Richard, J. P.; Amyes, T. L.; Vontor, T. *J. Am. Chem. Soc.* **1992**, *114*, 5626-5634.
103. Richard, J. P.; Amyes, T. L.; Vontor, T. *J. Am. Chem. Soc.* **1991**, *113*, 5871-5873.
104. Kandanarachchi, P.; Sinnott, M. *J. Am. Chem. Soc.* **1994**, *116*, 5592-5660.
105. Davies, C. W. *Ion Association;* Butterworths: Washington, 1962; pp 77-87.
106. Richard, J. P. *J. Org. Chem.* **1992**, *57*, 625-629.
107. Ritchie, C. D.; Wright, D. J.; Huang, D.-S.; Kamego, A. A. *J. Am. Chem. Soc.* **1975**, *97*, 1163-1170.
108. Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 4731-4732.
109. Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451-464.
110. Ta-Shma, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 8040-8050.
111. Gandler, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 8218-8223
112. Bunton, C. A.; Davoudazedeh, F.; Watts, W. E. *J. Am. Chem. Soc.* **1981**, *103*, 3855-3858.
113. Bunton, C. A.; Carrasco, N.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1267-1273.

114. Hill, E. A.; Mueller, W. J. *Tetrahedron Lett.* **1968**, 2565-2569.
115. Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581-603.
116. Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1396-1401.
117. Bergstrom, R. G.; Cashen, M. J.; Chiang, Y.; Kresge, A. J. *J. Org. Chem.* **1979**, *44*, 1639-1642.
118. Richard, J. P. *J. Chem. Soc., Chem. Commun.* **1987**, 1768-1769.
119. Winstein, S.; Robinson, G. C. *J. Am. Chem. Soc.* **1958**, *80*, 169-181.
120. Harris, J. M. *Prog. Phys. Org. Chem.* **1974**, *11*, 89-173.
121. Pienta, N. J.; Kessler, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 2419-2428.
122. Pienta, N. J.; Kessler, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 8330-8339.
123. Cournoyer, M. E.; Jørgensen, W. L. *J. Am. Chem. Soc.* **1984**, *106*, 5104-5112.
124. Jørgensen, W. L. *J. Am. Chem. Soc.* **1977**, *99*, 280-283.
125. Arnett, E. M.; Hofelich, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2889-2895.
126. Arnett, E. M.; Pienta, N. J. *J. Am. Chem. Soc.* **1980**, *102*, 3329-3334.
127. Bentley, T. W.; Schleyer, P. v. R. *Adv. Phys. Org. Chem.* **1977**, *14*, 1-67.
128. Bentley, T. W.; Carter, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 5741-5747.
129. Liu, K.-T.; Chang, L.-W.; Chen, P.-S. *J. Org. Chem.* **1992**, *57*, 4791-4793.
130. Wolf, J. F.; Abboud, J. L. M.; Taft, R. W. *J. Org. Chem.* **1977**, *42*, 3316-3317.
131. Richard, J. P.; Jagannadham, V.; Amyes, T. L.; Mishima, M.; Tsuno, Y. *J. Am. Chem. Soc.* **1994**, *116*, 6706-6712.
132. Taagepera, M.; Henderson, W. G.; Brownlee, R. T. C.; Beauchamp, J. L.; Holtz, D.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 1369-1370.
133. Taagepera, M.; Summerhays, K. D.; Hehre, W. J.; Topsom, R. D.; Pross, A.; Radom, L.; Taft, R. W. *J. Org. Chem.* **1981**, *46*, 891-903.
134. Mayr, H; Patz, M. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 938-957.

(*Received* 18 *August* 1994)